OPTION B+ IN MALAWI: ANTIRETROVIRAL THERAPY FOR PREVENTION OF MOTHER-TO-CHILD HIV TRANSMISSION AND ITS EFFECTS ON PRETERM BIRTH AND FEMALE-TO-MALE HIV TRANSMISSION

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ABSTRACT

Maganizo Brave Chagomerana: Option B+ in Malawi: Antiretroviral therapy for prevention of mother-to-child HIV transmission and its effects on preterm birth and female-to-male HIV transmission
(Under the direction of Kimberly A. Powers)

Large number of new and prevalent HIV infections among reproductive-aged women in sub-Saharan Africa makes prevention of mother-to-child HIV transmission (PMTCT) a major public health priority. Option B+ is a simplified approach to PMTCT that recommends universal life-long ART for pregnant and breastfeeding women regardless of HIV disease stage or CD4 count. This approach is expected to help bring an end to new pediatric HIV infections and substantially improve maternal health in settings with high HIV burdens. However, the effect of ART initiation during pregnancy in the Option B+ era on birth outcomes and female-to-male HIV transmission is not well known.

We used maternity-ward data from Bwaila Hospital in Lilongwe, Malawi to estimate the risk of preterm birth among HIV-infected women. The risk of preterm birth was similar in women who had initiated ART at any point prior to delivery compared to those who never initiated ART (adjusted Risk Ratio (aRR) = 0.88; 95% CI: 0.65 – 1.19). No clear trend between timing of ART and risk of preterm birth was observed. ART initiation at any point before delivery was strongly protective against extremely to very preterm birth (27 – 32 weeks gestation) (aRR = 0.43; 95% CI: 0.26 – 0.72)

Using mathematical modeling we estimated the female-to male HIV infections using two PTMTC approaches, Option B and Option B+ in the period 2011 - 2020. The estimated relative incidence (RI) under Option B+ was 4% lower (median RI = 0.96; 95% CI: 0.94 – 0.97) in 2015

and was projected to be 7% lower (median RI = 0.93; 95% CI: 0.90 – 0.95) by 2020 compared to the Option B in which ART uptake values in the period 2011-2020 assumed to be the same for Option B as those assumed for Option B+. When Option B ART uptake values in the period 2011-2020 were assumed to remain at 2011 levels, the estimated RI under Option B+ was 14% lower (median RI = 0.86; 95% CI: 0.84 – 0.88) in 2015 and was projected to be 21% lower (median RI = 0.79; 95% CI: 0.74 – 0.83) by 2020.

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LIST OF ABBREVIATIONS

AGA	Appropriate-for-gestational-age
ANOVA	One-way analysis of variance
aRR	Adjusted risk ratio
ART	Antiretroviral therapy
ARV	Antiretroviral
ATHENA	AIDS Therapy Evaluation in the Netherlands
AZT	Azidothymidine
AZT/3TC	Azidothymidine / lamivudine
CI_{E-}	Cumulative incidence among unexposed individuals
CI_{E+}	Cumulative incidence among exposed individuals
coRR	Confounding risk ratio
DAE	Differential algebraic equations
DAG	Directed acyclic graph
DeDE	Delay differential equations
DHS	Demographic and Health Survey
EMM	Effect measure modification
ICD-10	Classification of Diseases, 10th revision
IRB	Institutional Review Board
IUGR	Intrauterine growth restriction
IVP	Initial value problems
LBW	Low birthweight
LMP	Last menstrual period

LRT	Likelihood ratio test
MTCT	Mother-to-child transmission
NHSRC	National Health Sciences Research Committee
NVP	Nevirapine
ODE	Ordinary differential equations
OR	Odds ratio
PI	Protease inhibitor
PMTCT	Prevention of mother-to-child transmission
POC-EMRS	Point-of-care electronic medical record system
RR	Risk Ratio
sdNVP	Single dose nevirapine
SGA	Small-for-gestational-age
TDF/3TC/EFV	Tenofovir / lamivudine / efavirenz
uRR	Unadjusted risk ratio
WHO	World Health Organization

CHAPTER ONE: SPECIFIC AIMS

Mother-to-child HIV transmission (MTCT) can occur in-utero, intrapartum or postnatally during breastfeeding. Life-long triple antiretroviral (ARV) treatment for HIV-infected pregnant women with CD4 < 350 cells per mm^3, and prophylaxis (Option A) or ARV (Option B) during pregnancy for women with CD4 ≥ 350 cells per mm^3 starting as early as 14 weeks of gestation, has been successful in reducing MTCT.[1-4] However, the requirement to measure CD4 cell count to determine eligibility for starting treatment or stopping of treatment after breastfeeding has been a challenge in most resource-poor settings where CD4 cell count testing is not readily available.

In 2011, the Malawi government proposed and started implementing a new and simplified approach for prevention of mother-to-child transmission (PMTCT) called Option B+, in which all confirmed HIV-infected pregnant or breastfeeding women are started on antiretroviral therapy (ART) for life regardless of World Health Organization (WHO) clinical stage or CD4 cell count.[5] Since the introduction of PMTCT Option B+ in Malawi, the number of pregnant or breastfeeding women on ART has dramatically increased.[6,7] WHO now recommends the Option B+ strategy to all countries with a generalized HIV epidemic.[8] Besides preventing vertical transmission, the Option B+ program has other potential ancillary benefits. When properly adhered to, ART can improve infant and maternal health, prevent sexual HIV transmission, and prevent MTCT in subsequent pregnancies.[9-11]

The Option B+ program in Malawi has now matured, providing an opportunity to assess the relationship between time of ART initiation during pregnancy and birth outcomes and to evaluate the ancillary benefit of lifelong ART for pregnant and breastfeeding women on female-to-male HIV transmission (as compared to more limited-duration ART under the Option B

approach). This assessment will help to define the optimal time for ART initiation among pregnant women and quantify the ancillary benefit of lifelong ART under Option B+ on heterosexual HIV transmission in Malawi and similar countries planning to start Option B+.

Aim 1: Determine the effect of ART initiation during or before pregnancy on preterm birth among pregnant women in the Option B+ era.

Hypothesis: We hypothesize that a) HIV-infected pregnant women who initiate ART during or before pregnancy have a lower risk of preterm delivery than women who are not on ART during pregnancy, and b) earlier ART initiation is associated with a lower risk of preterm birth than is later ART initiation.

Overview: We will conduct a secondary analysis of data collected at delivery from HIV-infected women delivering at ≥ 27 weeks of gestation between April 1, 2012 and November 15, 2015 at Bwaila Hospital in Lilongwe, Malawi. Among women on ART at delivery, we will restrict our analysis to women who initiated ART before 27 weeks of gestation. The outcome of interest will be preterm birth, defined as live birth at ≥27 and <37 weeks of gestation. The primary exposures will be ART use and time of ART initiation (never, before pregnancy, 1st trimester, 2nd trimester). We will use log-binomial regression models to estimate the preterm birth risk ratios comparing women who were on ART during delivery (and according to time of ART initiation) to women who never initiated ART.

Aim 2: Develop a mathematical model to quantify the ancillary benefit of Option B+ (relative to Option B) on heterosexual transmission in Lilongwe, Malawi.

Hypothesis: Life-long ART initiated among HIV-infected pregnant women under Option B+ can reduce the incidence of HIV in the general population through reduced transmission from HIV-infected women to HIV-uninfected men during and beyond the period of pregnancy and breastfeeding.

Overview: We will develop a deterministic mathematical model to study the effect of Option B+ on female-to-male HIV transmission among sexually active women aged 15 – 49 years in Lilongwe, Malawi. The model will describe the dynamics of HIV infection and progression, HIV treatment, and pregnancy and breastfeeding according to age and calendar time among sexually active women. HIV transmission to men will be specified as a function of female HIV prevalence and the relative infectiousness of HIV according to disease stage, pregnancy status, and treatment status, allowing comparison of estimated female-to-male transmission under Option B+ versus Option B. .

CHAPTER TWO: BACKGROUND AND SIGNIFICANCE

The burden of HIV / AIDS in sub-Saharan Africa

In 2013, an estimated 24.7 million people in sub-Saharan Africa were living with HIV, accounting for 71% of the estimated HIV-infected population worldwide. Of the 24.7 million adults and children living with HIV, 1.5 million were newly infected, reflecting high HIV incidence in this setting. The HIV pandemic in the region has disproportionately affected women; 58% of people living with HIV in sub-Saharan Africa are women.[12] The high HIV prevalence among women, the majority of whom are reproductive-aged, has resulted in substantial maternal morbidity and mortality, adverse birth outcomes, and mother-to-child HIV transmission.

Maternal morbidity and mortality

HIV is the leading cause of death among women during pregnancy and the postpartum period in sub-Saharan Africa. At least 25% of all pregnancy-related deaths in the region have been attributed to HIV infection.[13] In 2010, sub-Saharan Africa contributed about 56% to the total global maternal deaths. 17,000 of these maternal deaths in sub-Saharan Africa were attributed to HIV, representing 91% of all HIV-related maternal deaths in the world.[14,15]

The exact cause of maternal mortality among women with HIV/AIDS is still unclear. HIV-infected women with a low CD4 cell count during pregnancy or postpartum are more likely to die compared to women with higher CD4 cell counts.[16] Maternal HIV infection during pregnancy decreases the percentage and absolute number of CD4 cells.[13] The decrease in CD4 cell count may result in a greater risk of opportunistic infections not related to pregnancy, leading to fast HIV disease progression and eventually death. Faster HIV disease progression in pregnancy

(vs. not during pregnancy) is more common in developing countries (OR = 3.71; 95% CI: 1.82 - 7.75) compared to developed countries (OR = 0.55; 95% CI: 0.27 - 1.11).[17] Poor nutrition and limited access to health care during pregnancy are some of the factors modifying the association between pregnancy and HIV disease progression in developing (versus developed) countries.[18,19]

Adverse pregnancy outcomes in HIV-infected women

Adverse birth outcomes, including preterm births, stillbirths, and low birthweight births, can be physically and emotionally devastating to the mother. Maternal nutritional status before and during pregnancy has been the major determinant of gestational outcomes worldwide.[20-22] In areas where poor nutrition is common, the prevalence of adverse birth outcomes is generally high. For example, more than 60% of preterm babies worldwide are born in low-income countries of south Asia and sub-Saharan Africa.[23]

Preterm birth

Preterm birth, often defined as being born before 37 weeks of gestation, is the second-leading cause of death in children under 5 years, and the single most important cause of death within the first month of life.[24] Worldwide, preterm births account for 75% of all perinatal mortality.[25,26] Out of the estimated 15 million infants born preterm in 2010, more than 1 million died as a result of being born premature.[23,27]

Very little is known about the causes and mechanisms of preterm birth.[27] In areas where HIV is endemic, HIV infection during pregnancy has emerged as a major risk factor for preterm birth. In sub-Saharan Africa, the risk of having a premature baby among HIV-infected women has been estimated to be at least double the risk of having a premature baby among HIV-uninfected women.[28-30]

Stillbirths

Stillbirths constitute the majority of the world's perinatal deaths. In 2009, at least 2.64 million stillbirths (range 2.14 million to 3.82 million), defined as ≥1000g birthweight or ≥28 weeks of gestation, were estimated to have occurred worldwide. Of the 2.64 million stillbirths, more than 76% occurred in South Asia and sub-Saharan Africa, where skilled birth attendants and access to caesarean sections are much lower than in developed countries. In sub-Saharan Africa alone, 934,600 of the 33 million estimated total births in 2009 were stillbirths.[31]

While fewer skilled birth attendants and lack of facilities for caesarean sections are contributing to the large number of stillbirths in sub-Saharan Africa,[32] the high prevalence of HIV among reproductive-aged women may also be contributing to the increase in the number of stillbirths. Studies in the region have found that the risk of having a stillbirth is higher among HIV-infected women compared to HIV-uninfected women.[28] In a meta-analysis investigating the association between maternal HIV infection and perinatal outcomes, the odds of having a stillbirth among HIV-infected women was found to be at least three times the odds of having a stillbirth among HIV-uninfected women (OR = 3.91; 95% CI: 2.65 - 5.77).[33]

Low birthweight

Low birthweight (LBW) is not only an important risk factor for neonatal mortality but also a major determinant of post-neonatal infant mortality and infant and childhood morbidity.[25] A newborn baby is marked as having LBW when it weighs less than 2500g within the first hour of life, irrespective of gestational age. Globally, more than 20 million infants are born with LBW; 95.6% of these infants are born in the developing countries. The developing regions of Asia and Africa contribute 92% of all LBW babies born in developing countries.[34]

LBW is caused by short gestational period (preterm birth), intrauterine growth restriction (IUGR) or a combination of preterm birth and IUGR.[20,21] Whether the infants are preterm or not, IUGR results in infants who are small-for-gestational-age (SGA). While LBW is defined as

infants who weigh < 2500g at birth, SGA is based on the percentile of the birthweight-for-gestational age; defined as birthweight below the10th percentile of the expected birthweight for any growth week. Infants with prematurity-related LBW have an increased risk of developing conditions that are related to physiological immaturity compared to those with IUGR related LBW. Most infants born with IUGR-related LBW show growth and subtle neurological cognitive deficiencies.[20] In general, SGA infants have poorer outcomes than appropriate-for-gestational-age (AGA) infants.[35]

The prevalence and causes of LBW vary in different regions of the world. Developing countries have a higher prevalence of LBW than developed countries. While most of the LBW are due to preterm birth in developed countries, in developing countries LBW is often associated with IUGR.[36] In sub-Saharan Africa, where the prevalence of HIV infection is also high, HIV infection has been associated with both LBW and SGA.[28-30,37-40] For example, in a case-control study of 177 HIV-seropositive and 326 seronegative women and their newborns in Nairobi, Kenya, the birthweight was less than 2500 g in 9% of cases and 3% of controls (OR = 3.0; 95% CI: 1.3 - 6.7).[39] In South Africa, the risk ratio of having SGA infants when HIV-infected women were compared with HIV-uninfected women was estimated to be 1.28 (95%CI: 1.6 - 1.53).[40]

Risk factors for adverse birth outcomes among HIV-infected pregnant women

In addition to other established risk factors associated with adverse birth outcomes such as socioeconomic status, ethnicity, multiple pregnancy, parity, substance abuse, intrauterine infections, and infection with sexually transmitted diseases, [20,26,41] high HIV viral load and low CD4 cell count are known to increase the risk of adverse pregnancy outcomes among HIV-infected pregnant women.

Without HIV treatment, the level of HIV viral load and CD4 cell count varies over the course of HIV infection. In a typical course of HIV infection, there is a widespread dissemination of the virus and a sharp decrease in CD4 cell count in peripheral blood during primary infection.

When the immune system starts to respond to the infection, the levels of detectable viremia start to decrease. After several weeks, the CD4 cell count starts to decrease again and this continues until it reaches a critical low level below which the HIV virus starts to replicate and spread again.[42] The primary and late stage periods of HIV infection, characterized by high viremia, are particularly high-risk periods for poor birth outcomes among HIV-infected women.

Among HIV-infected pregnant women, high HIV viral load significantly increases the risk of having a stillbirth. The risk of having a stillbirth among HIV-infected pregnant women with high viral load can be at least twice the risk of having a stillbirth among HIV-infected pregnant women with low viral load.[43,44] HIV viral load has also been observed to have a similar effect on preterm birth and LBW.[45]

Low CD4 cell count among HIV-infected pregnant women has also been associated with a significant increase in adverse birth outcomes. Studies of neonates from HIV-seropositive women in Sub-Sahara Africa have shown that mothers with low CD4 cell count were more likely to have infants with LBW compared to mothers who had higher CD4 cell count.[39] Similar associations have been observed between CD4 cell count and stillbirth or preterm birth.

Issues in measuring birth outcomes

Accurately counting adverse birth outcomes is important for public health. These statistics provide an opportunity to set targets for interventions towards improving maternal and child health. However, measuring incidence or prevalence of birth outcomes and comparing them across countries has been a challenge. In particular, inconsistences in the definitions of birth outcomes and the use of different measurement approaches for the same outcomes in different countries have made comparison of birth outcome statistics difficult.

Gestational age is an important factor in predicting date of delivery and identifying preterm or SGA infants. Unfortunately, in areas where ultrasound for dating pregnancy is not available, the gestational age is often inaccurate.[46] In the absence of ultrasound for dating

pregnancy, last menstrual period (LMP) and lunar or menstrual cycles have been used. The use of date of LMP as the onset of pregnancy is prone to recall bias, as many women do not know the exact date they last had a menstrual period. In a study of infants born extremely preterm (< 28 weeks) in the Swedish national registry, gestational age estimated by LMP for extremely preterm infants appeared to be longer than gestational age estimated by ultrasound (17.2% of the gestational ages measured by LMP were longer than 27 weeks).[47] Other variants of months used in some countries in counting duration of pregnancy such as lunar or menstrual cycles make correct calculation of pregnancy duration difficult.

Although stillbirths constitute the majority of the world's perinatal deaths, statistics on stillbirth are largely missing in most country or world health reports. In most developing countries, 80% of stillborn babies are disposed of without any recognition,[46] resulting in fewer stillbirths recorded than actually observed worldwide.

Different countries use different measures and cut-offs to classify a fetal death as stillbirth. According to International Classification of Diseases, 10th revision (ICD-10), a stillbirth is defined as any fetal death in the last two trimesters of pregnancy that satisfies any of the following three criteria: has a birthweight ≥500g, completed ≥ 22 weeks of gestational age, or has crown-heel length ≥ 25 cm. On the other hand, WHO defines any fetal death as stillbirth if it satisfies any of the following three criteria: has birthweight ≥ 1000g, completed ≥28 weeks of gestation, or has body length ≥ 35cm. In some developed countries, fetal deaths as early as 18 weeks are defined as stillbirths.[48,49]

The reported number of stillbirths therefore can vary depending on the measure and cut-off used in defining stillbirth. The use of weight, gestational age, or body length in classifying stillbirths may result in different counts of stillbirths. Even among those that use gestational age, the use of different gestational age cut-offs for defining stillbirth makes comparison of stillbirths across the world difficult. The use of a much higher gestational age or much lower gestational age in defining stillbirths can result in underestimating or overestimating stillbirths respectively.[50]

LBW is an important factor in determining neonatal mortality and post-neonatal quality of life.[51] However, worldwide estimates of incidence or prevalence of LBW are often unrepresentative. In sub-Saharan Africa, more than 40% of babies are born at home and without a skilled birth attendant, resulting in many infants that are not weighed. Among the live births that are weighed, not all weight is measured within the first hour of life before significant postnatal weight loss has occurred. In addition to failure to weigh new born babies within the recommended period, different scales have been used to weigh new born babies. The use of different scales has contributed to distortion and errors in measuring birthweight. These inconsistences and errors are more common when the scales are not well calibrated or the readings are always rounded, as is the case where categorical scales are used. Although the use of chest circumference as a proxy measure for birthweight is recommended for babies that are not delivered at a health facility, it does not provide an accurate measure for birthweight.[34]

There is a need to correctly classify LBW as either preterm SGA or term SGA. Correctly classifying LBW infants as preterm SGA and term SGA infants is important in studying the risk factors and understanding the prognosis associated with LBW. The difficulty in separating preterm infants, preterm SGA infants and term SGA infants has resulted in the incorrect comparison of risk factors for preterm birth and SGA births. While some studies have excluded preterm SGA infants in a study of the risk factors for preterm births compared with SGA births,[52] others have included preterm SGA births in both preterm birth and SGA births.[53,54]

HIV mother-to-child transmission

In 2011, 330,000 children acquired HIV infection worldwide. Among the children who acquired HIV infection in 2011, more than 90% lived in sub-Saharan Africa.[55] The majority of HIV infections among children are acquired from their mothers during pregnancy, delivery or breastfeeding. In the absence of any intervention, approximately 13%–43% of the children born

to HIV-infected mothers are infected by the virus, depending on setting and duration of breastfeeding.[56]

The exact timing for vertical transmission during pregnancy is not well understood. While a few studies have reported vertical transmission as early as the first trimester,[57,58] the majority of studies have reported the occurrence of fetal infections during the second trimester or later.[59-61] When identifying prenatal transmission, it is often difficult to differentiate in utero from intrapartum transmissions. However, based on the time when HIV infection was detected in infants who were not exposed to breast milk (first two days of life versus after one week of life and by 6 weeks of age), about two thirds of perinatal vertical transmission appear to occur during labor.[62-64]

Risk factors for HIV MTCT

HIV MTCT is either due to existing HIV infection at conception or incident infection during pregnancy or breastfeeding. While some risk factors for HIV MTCT apply to all times of transmission, others are specific to prenatal, during labor and delivery or postnatal periods.

HIV viral load and immunological status of an HIV-infected woman during pregnancy, delivery or breastfeeding influences HIV vertical transmission. Higher maternal viral load in plasma, genitourinary tract or breast milk has been associated with a higher risk of vertical HIV transmission.[65-68] Maternal immunological status has also been shown to influence the MTCT of HIV in both pregnant and breastfeeding women; lower maternal CD4 cell count has been shown to be associated with an increased risk of both perinatal and postnatal HIV MTCT.[66,69-71]

Infection with other sexually transmitted diseases in HIV-infected women increases the risk of HIV MTCT.[72,73] The increase in risk may be due to enhanced HIV replication or effects of infection such as cervicitis, genital ulcers and chorioamnionitis. Rapid HIV replication may increase the viral load in the genital tract[74] resulting in increased risk of transmission during pregnancy and delivery. Increased viral load in the presence of cervicitis and genital ulcers may

increase the risk of both intrauterine and intrapartum HIV transmission (especially in vaginal deliveries). Compromised integrity of the placental barrier by chorioamnionitis may facilitate free transfer of HIV across the placenta and may lead to HIV transmission intrapartum.[70]

Premature infants born to HIV-infected women have an increased risk for HIV infection compared to full term infants.[30,70,75-77] In a prospective study of pregnant women infected with HIV, infants born at 37 weeks of gestation or earlier were at higher risk of HIV-1 infection than infants born at 38 weeks of gestation or later (60% vs 22%).[77] Since transfer of maternal antibodies to the fetus occurs late in pregnancy, most preterm infants are born before the adequate levels of maternal antibodies have been transferred.[78] In HIV-infected pregnant women, such preterm infants are therefore more likely to be infected with HIV during delivery.

During vaginal delivery, infants born to HIV-infected women are exposed to contaminated blood or cervical secretions.[74] The exposure to contaminated blood and cervical fluids increases the risk of HIV transmission during the intrapartum period. A European study of singleton births of HIV-infected women showed that infants delivered through caesarean section have a lower risk of being infected with HIV than those delivered through the vagina (3.4% vs 10.2%).[75] In addition to exposure to blood and cervical fluids during vaginal delivery, prolonged duration of membrane rupture may be an important factor in HIV-transmission.[63,76,79] This can explain why in a study of twins, the first born twin was more likely to be infected with HIV than the second-born twin.[80]

In most sub-Saharan Africa countries, breastfeeding is strongly encouraged for the first 24 months of life because it satisfies the nutritional needs of the infant and helps to protect the infant against diarrheal and upper respiratory infections and deaths.[81,82] Unfortunately, free HIV and HIV DNA are detected in breast milk of HIV-infected mothers.[83,84] As a result, postnatal vertical transmission of HIV from mother to the child is more common in children who are breastfed compared to those who are not.[71,85,86] In the absence of any intervention, breastfeeding by an infected mother increases the risk of mother-to-child transmission from

15%–30% in non-breastfeeding populations to 20%–45% in those who breastfeed.[87] The lack of substitutes for breast milk in developing countries has therefore made the task of balancing the risk of HIV MTCT through breast milk against the substantial benefits of breastfeeding very challenging.

Among infants who are breastfeeding, the risk of vertical HIV transmission depends on the duration of breastfeeding, the time when the mother seroconverted, and the presence of some clinical diseases. In Malawi and Tanzania, prolonged breastfeeding for about 2 years has been shown to increase the cumulative risk of HIV MTCT to as high as 15%.[88,89] A meta-analysis comparing rates of infection between infants of women who seroconverted postnatally versus infants of women whose HIV-infection was confirmed during delivery, infants whose mothers seroconverted postnatally had a higher risk of acquiring HIV (Risk = 29%; 95% CI: 16 - 24%) compared to the risk for infants whose mothers' HIV-infections were confirmed at delivery (Risk = 14%; 95% CI: 7 - 22%).[85] Similarly, a prospective study of HIV-infected mothers who were either HIV-seropositive at delivery and whose infant tested HIV negative at six weeks (HIV exposed) or HIV-seronegative at delivery and whose infant also tested HIV-negative at six weeks showed that the breastfeeding-associated risk of HIV transmission was 2.9 times as high among women who seroconverted postnatally compared to women who were HIV-seropositive at baseline (delivery).[90] The occurrence of clinical diseases such maternal mastitis and nipple lesions during breastfeeding also increases the risk of vertical HIV transmission.[66,91,92]

Prevention of HIV mother-to-child transmission

PMTCT has been a dynamic and rapidly changing field. Since the early days of the HIV epidemic, several interventions have been tried to prevent the vertical transmission of HIV. These interventions included washing the birth canal,[93] antenatal supplementation with vitamin A,[94] and treatment of chorioamnionitis.[95] Although these interventions had maternal and child health benefits, and were quick to implement in poor countries due to low cost, they lacked

efficacy in reducing HIV MTCT.[96] Since antiretroviral prophylactic drugs were shown to be effective in reducing HIV MTCT in the developed world,[97] a lot of effort has been made to ensure that the drugs are available to all HIV-infected pregnant and breastfeeding women worldwide.

WHO issued the first recommendations for the use of ARV drugs for PMTCT in 2000 [98] to harmonize the implementation of PMTCT programs. Over time, these recommendations have been revised [99-102] as simplified and standardized regimens, and more potent ARV prophylaxis regimens, have become available. The changes were also necessitated by the availability of evidence on the effectiveness of ARVs in preventing MTCT, safety of ARV drugs for pregnant women, and drug resistance following ARV prophylaxis among pregnant women and its implications for future treatment options.

Treatment options for PMTCT programs

Currently, WHO lists three options for PMTCT: Option A, Option B and Option B+.[8] Both Options A and B recommend triple ARVs for HIV-infected women with CD4 cell count < 350 cells per mm^3, and prophylaxis for HIV-infected pregnant women with CD4 cell count ≥ 350 cells per mm^3 as early as 14 weeks of gestation. For women with CD4 cell count ≥ 350 cells per mm^3, Option B uses triple ARVs as prophylaxis for women with CD4 ≥ 350 cells per mm^3 throughout antepartum and to 1 weeks after breastfeeding cessation (for those breastfeeding). Under Option A, pregnant women with CD4 cell count ≥ 350 cells per mm^3 use azidothymidine (AZT) throughout antepartum, single dose nevirapine (sdNVP) plus first dose of azidothymidine / lamivudine (AZT/3TC) during labor, and daily AZT/3TC through 7 days of postpartum. Option B+ recommends offering lifelong triple ART to all confirmed HIV-infected pregnant or breastfeeding women regardless of their WHO clinical stage or CD4 cell count. Option B and Option B+ ensure that HIV-infected pregnant women receive fully suppressive triple ART regimen during pregnancy. While treatment for infants born to HIV-infected women depends on infant feeding method (daily nevirapine (NVP) until 1 week after cessation of breastfeeding or

daily NVP through age 4-6 weeks if not breastfeeding) under Option A, both Option B and Option B+ recommends infants to receive daily NVP or AZT from birth through age 4-6 weeks regardless of infant feeding method .[11,102]

Benefits of Option B+ over Option A and Option B

Besides preventing mother-to-child HIV transmission, the Option B+ approach has the potential to improve the operations of PMTCT programs, improve maternal health beyond pregnancy, and reduce HIV transmission from HIV-infected women to their sexual partners.[5,102]

HIV pregnant women need to receive a fully suppressive triple ARV regimen so that the risk of infant infection is minimized and their own health benefit is maximized during pregnancy. However, linking PMTCT program access to CD4 cell count testing to determine eligibility has been a major challenge for increasing uptake of PMTCT programs in resource-constrained settings.[5] The Option B+ strategy offers an escape from the CD4 cell count testing requirement for determining treatment eligibility under Option A and Option B. This break in the link between PMTCT and CD4 cell count testing under Option B+ has simplified the PMTCT program requirements and increased ART uptake during pregnancy. Additionally, under Option B+, all women continue ART after breastfeeding cessation, whereas under Option B, only those women with CD4 counts below treatment eligibility thresholds continue ART.

In sub-Saharan Africa, almost 60% of the region's HIV infections are among reproductive-aged women (ages 15-49 years).[55] These relatively young HIV-infected women are likely to get pregnant at least once, and in some countries, the pregnancy rate among HIV-infected women is comparable to the general population.[103] Among the HIV-infected women, the incidence of pregnancy ranges from 9 to 24.6 pregnancies per 100 person-years. Furthermore, HIV-infected women on ART are more likely to get pregnant than HIV-infected women not on ART.[103-105] Since Option B+ extends treatment beyond pregnancy and breastfeeding, it has the potential to protect the next pregnancy from HIV from its inception. Option B+ also avoids the

risks associated with stopping and re-starting triple ART among reproductive-aged women. Continuing on ART treatment beyond pregnancy and breastfeeding may improve maternal and child health by reducing the risk of opportunistic infections and deaths due to interrupted ART.

HIV viral load is one of the most important determinants of the risk of HIV transmission. Among heterosexual men and women in a community-based study in a rural district in Uganda, an adjusted seroconversion rate ratio of 2.45 (95% CI: 1.85 - 3.26) was associated with each log increment in the viral load.[106] ART has been shown to reduce HIV-1 concentration to undetectable level in the plasma,[107,108] semen [109,110] and cervicovaginal[108] among people receiving ART. As a result of the decline in HIV-1 concentrations, ART had been proven to prevent mother-to-child transmission[97,111] and reduce HIV transmission among adults in ecological studies, observational cohort studies and randomized clinical trials. A reduction in HIV transmission among serodiscordant couples has been shown in systematic reviews and meta-analyses of observational studies comparing sexually engaged serodiscordant couples receiving ART with those not receiving ART.[112,113] The HPTN 052 study, a randomized clinical trial of HIV serodiscordant partners, showed that counselling and earlier initiation of ART reduced linked HIV transmissions by 96.4%.[114]

A number of mathematical models have been developed to assess the impact of treatment as prevention on generalized epidemics. In a systematic comparison of 12 models that were developed to evaluate a set of standardized ART intervention scenarios in South Africa, all models suggested that ART, at high levels of access and with high adherence, has the potential to substantially reduce new HIV infections.[115] An interesting finding from one of the models that was included in the comparison is that universal voluntary HIV testing with immediate ART as a strategy would lead to an HIV elimination phase within 5 years.[116]

Realizing the potential impact of treatment as prevention, WHO issued recommendations on the strategic use of antiretrovirals to help end the HIV epidemic that encourages countries to consider expanding ART to subpopulations that include pregnant

women and serodiscordant couples regardless of CD4 cell count.[117] These guidelines have been continually revised to recommend ART initiation at earlier infection stages as evidence for the clinical and prevention benefits of early treatment has mounted. The recommendations aim at ensuring that ART is not only having health benefits but also prevention impact. Although the main purpose of Option B+ is for PMTCT, Option B+ also has the potential for continued prevention of sexual HIV transmission in serodiscordant couples or partners by extending ART beyond pregnancy and breastfeeding. However, the impact of Option B+ on the HIV epidemic through reduced heterosexual transmission has not been quantified in Malawi, the first country to implement this strategy.

Optimal timing for ART initiation during pregnancy

The effect of ART exposure during pregnancy on fetal development is still unclear. In studies comparing adverse birth outcomes between infants exposed to ART and those not exposed to ART during pregnancy, some have shown an increased risk of preterm birth, LBW or stillbirths among those exposed to ART,[118-122] while others have shown no difference[123] or improved outcomes.[124] The timing of ART initiation for pregnant women may also have implications for the development of the fetus. In a cohort study comparing preterm delivery and LBW between women who used ART pre-conception and those who initiated ART during pregnancy, ART used in pre-conception was associated with an increased risk for preterm births and LBW.[125,126] For infants who were exposed to ART during pregnancy, early exposure (exposed <28 weeks gestation) was associated with an increased risk of preterm birth compared to late exposure (exposed ≥28 weeks).[118]

While these findings show that there is some risk associated with early ART exposure during pregnancy on birth outcomes, the results are not conclusive. These findings do not elucidate the optimal time to initiate ART among HIV-infected pregnant women in order to minimize adverse pregnancy outcomes. Since there is also evidence that early exposure to ART

during pregnancy is associated with reduction in HIV MTCT,[127,128] there is a need to determine an optimal time to initiate ART among pregnant women that will be effective in maximizing reduction in transmission while minimizing adverse birth outcomes.

CHAPTER THREE: RESEARCH DESIGN AND METHODS

Aim 1: Time of ART initiation and preterm birth

Study Design

To estimate the association between time of ART initiation during pregnancy and risk of preterm birth, we conducted a retrospective cohort study among HIV-infected pregnant women delivering a singleton live birth at Bwaila Hospital in Lilongwe, Malawi from April 1, 2012 through November 15, 2015. The data we used were collected and entered into a Point-of-Care Electronic Medical Records System (POC-EMRS) database at the time of delivery.

Study population

In Malawi, pregnant women attending antenatal clinics undergo HIV counselling and rapid HIV testing using the opt-out approach:[129] an HIV test is performed after notifying the pregnant woman that the test is routinely performed, but that she may elect to decline or defer testing. All pregnant women who test for HIV are asked to provide locator information to be used for contact in the event of abnormal test results. Until July 2011, all confirmed HIV-infected pregnant women were required to undergo CD4 count testing to determine if they were eligible for ART. Based on WHO recommendation for HIV-infected pregnant women, pregnant women with CD4 <350 or WHO Clinical Stage 3 or 4 were eligible to start ART. HIV-infected pregnant women with CD4 counts ≥350 cells received single dose nevirapine (NVP) for PMTCT under "Option A" or a combination regimen under "Option B". Since the adoption of Option B+ in July 2011, confirmed HIV-infected pregnant women are no longer required to undergo CD4 cell count testing to determine if they are eligible for ART. HIV-infected pregnant women are initiated

on ART for life regardless of CD4 cell count or WHO clinical stage as soon as they are diagnosed. As our study was conducted in the "Option B+ era," all pregnant women in the study population were eligible for lifelong ART.

To limit confounding due to the intrinsic link between length of gestation and ART duration during pregnancy, we constructed our study population such that the risk period for the outcome (preterm birth) was entirely separate from the eligible ART start times. Specifically, we restricted our analysis to women who: a) delivered on or after 27 weeks of gestation, and b) either started ART before 27 weeks or did not receive ART at all prior to delivery. Additional details about this approach are included in Chapter 4.

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Exposure Assessment

HIV-infected women in the cohort were classified according to their ART exposure status at the time of delivery. For women who were on ART at delivery, we further classified them based on the time that they started ART: 1) before pregnancy (on ART at conception), 2) during the 1st trimester, or 3) during the 2nd trimester (<27 weeks of gestation).

Outcome assessment

Preterm births were identified based on the reported date of last menstrual period (LMP) and date of delivery. We classified a newborn baby as preterm if the baby was born alive and the birth occurred at or after 27 weeks of gestation and before 37 weeks of gestation (27 - < 37 weeks). Births occurring at 37+ weeks were considered full term.

Covariates assessment

We used a directed acyclic graph (DAG) to identify a minimally sufficient set of covariates to include in our analysis. All covariates that were collected and recorded in the maternity database during delivery were considered for inclusion in the DAG, with selection

further based on literature review and biological plausibility. The variables that were recorded included maternal age, education, gravidity, parity, and mode of delivery (spontaneous vaginal, vacuum extraction, breach, and caesarean section). Parity was preferred over gravidity for consideration as a confounder based on literature review.

After identifying the minimally sufficient set of potential confounders (mother's age, education and parity), we explored the best way of modeling continuous variables so that they fit the data well. Polynomials were used to assess linearity of continuous variables. To check for a linear trend in the response, we divided the continuous variables into categories based on scientific knowledge or literature review. For a more flexible assessment of the functional form of the continuous independent variables, we used both linear and quadratic spline models. Linear spline models allow the slope of the dose-response to change at each knot, while quadratic spline models allow the shape and direction of the dose-response curve to change at each knot. Goodness of fit for polynomial and spline models was assessed using likelihood ratio test (LRT). Based on this process, we included maternal age as a linear term in our model, and parity as ordinal.

Statistical analyses

Descriptive Analysis

Descriptive data analysis was used to assess variable distributions and detect outliers or influential observations. We estimated means (and standard deviations) and medians (and interquartile ranges) of continuous variables, and proportions of categorical variables. In addition, we examined the distributions of continuous variables using boxplots, histograms and scatterplots.

We also assessed the frequency of missing values for all variables including the main exposure and outcome. All observations with missing main exposure or outcome were excluded from the analysis. Mother's education was missing from 95% of records, and was thus excluded

from the analysis despite being among our minimum set of covariates identified through the DAG. All continuous and ordinal explanatory variables were assessed for collinearity using correlation coefficients. A correlation coefficient ≥ 0.5 was considered indicative of a strong correlation.

Fisher exact tests were used to asses differences in the distribution of categorical covariates between the outcome categories (preterm or full term) as well as across the exposure categories (ART initiation: before pregnancy, 1st trimester, 2nd trimester, or never initiated). T-test and one-way analysis of variance (ANOVA) was used to test differences in means between the outcome categories and across the exposure categories respectively.

Multivariable analysis

To estimate the association between ART use and preterm birth, and between time of ART initiation and preterm birth, we used log-binomial regression to calculate both unadjusted and adjusted risk ratios and the corresponding 95% confidence limits. Using log-binomial regression allowed us to take into account the effect of confounders on the relationship between ART exposure and risk of preterm birth.

The risk ratio (RR) is the cumulative incidence (CI_E) of the outcome (D+) among the exposed (E+), divided by the cumulative incidence (CI_{E-}) of the outcome (D+) among the unexposed (E-), for a fixed period of time.

$$RR = \frac{CI_E}{CI_{E-}} \qquad (1)$$

Log-binomial regression assumes a linear relationship between the risk ratio and the covariates on the log scale and can be expressed follows:

$$log[\, RR \mid (X, \boldsymbol{Z}) \,] = \alpha + \beta X + \gamma \boldsymbol{Z} \qquad (2)$$

where X is the exposure and $\boldsymbol{Z}$ is the covariate vector. Taking the exponent of equation (2), the RR can be expressed as:

$$RR|(X, \boldsymbol{Z}) = exp(\alpha + \beta X + \gamma \boldsymbol{Z}) \qquad (3)$$

In the multivariable log-binomial regression model scenario as presented in (2), the regression parameter β is the log risk ratio for a unit change in exposure variable X while holding the covariates vector $\boldsymbol{Z}$ constant at any level of $\boldsymbol{z}$ (not necessarily the same level for all $\mathbf{z}$ covariates). The exponent of β as in (3) is the risk ratio for a unit change in exposure variable X while holding the covariate vector $\boldsymbol{Z}$ constant at any level of $\boldsymbol{z}$**.**

Potential confounders identified through the DAG analysis were first assessed for effect measure modification (EMM) using a LRT with an a priori p-value of > 0.15. A full model with all of the covariates (including interaction terms) was compared to a reduced model containing all of the covariates in the full model except the interaction terms being assessed. Interaction terms resulting in LRT with p-value < 0.15 were retained in the model. None of the potential confounders were considered as EMM based on this criterion.

Finally, we evaluated the necessity of including the potential confounders in the multivariable model using the change-in-estimate approach. The change-in-estimate of the ln(RR) for preterm birth was calculated by comparing the absolute difference in the value of ln(RR) between a full model with all the covariates included and a reduced model with the

potential confounder being assessed excluded. The absolute difference was calculated as follows:

$$|ln(coRR)| = \left| \frac{ln(RR_{with\ covariates})}{ln(RR_{without\ covariates})} \right|$$

where *coRR* is the confounding risk ratio. As specified a priori, a potential confounder that resulted in ≥ 10% change in the estimate of ln(RR) after being excluded from the model was considered a strong confounder. Both mother's age and parity were retained in the model as strong confounders.

Sub analyses

The definition that we used for preterm, baby born alive and the birth occurred at or after 27 weeks of gestation but before 37 weeks of gestation, includes extremely preterm (< 28 weeks), very preterm (28 to < 32 weeks), moderate preterm (32 to < 34 weeks), and late preterm infants (34 to < 37 weeks). In order to assess the effect of time of ART initiation on each of these preterm gestational categories, we carried out three additional analyses. In the first model, we compared extremely to very preterm births with term births, excluding moderate to late preterm births. Second, we compared moderate to late preterm births with term births, excluding extremely preterm to very preterm births. In the third model, we compared extremely preterm to moderate preterm births (< 34 weeks) with late preterm to term births (≥ 34 weeks).

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

Aim 2: Option B+ and female-to-male HIV transmission

Study design

To estimate the expected relative reduction in HIV incidence among men over time under Option B+ compared to Option B, we used a deterministic, compartmental mathematical model to capture the population dynamics of women under the two PMTCT strategies. We then calculated HIV transmission under each strategy as a function of the numbers and relative infectiousness of HIV-infected women according to disease stage, ART status, and pregnancy status.

Study population

The model was based on the sexually active female population aged 15 – 49 years old in Lilongwe, Malawi. Malawi, one of the countries in sub-Saharan Africa with a high prevalence of HIV, has a population of 13.1 million (6.4 million males and 6.7 million females).[130] The HIV pandemic in Malawi has disproportionately affected women. In 2010, the prevalence of HIV was estimated to be higher among women (12.9%) than men (8.1%).[131] Besides heterosexual contact, vertical transmission of HIV to children who have been exposed to HIV during pregnancy or breastfeeding is also common.

We chose this study population because the main HIV transmission mode in Malawi is through heterosexual contact. In addition, Malawi was the first country to start implementing the PMTCT Option B+ program for all confirmed HIV-infected pregnant and breastfeeding women.

Model structure

We developed a deterministic, compartmental model to capture the population dynamics of women only. The model was stratified into compartments according to HIV status (HIV-uninfected, HIV-infected), age cohorts (15-19, 20-24, 25-34 and 35-49), and pregnancy /

breastfeeding status (not pregnant / breastfeeding, pregnant / breastfeeding). HIV infected women were further stratified by HIV disease stage based on CD4 cell count (CD4 ≥500, 350 ≤ CD4 ≤499, 200 ≤ CD4 ≤349, and CD4 < 200) and ART status (ART naïve, on ART, and ART drop-outs). Model equations are given in Appendix 1.

Population dynamics among women

Young women aged into the 15-19 years age group as HIV susceptible and without prior pregnancy. After entering into the model population, women could become infected with HIV, become pregnant, and age into the next older age category. HIV-infected women (pregnant or not) progressed through CD4 stages and could start ART treatment depending on the prevailing Malawi government guidelines for ART eligibility. Both HIV-negative and HIV-infected women were removed from the population through aging out of the sexually active population upon reaching 50 years of age. In addition, HIV-infected women were removed from the population through death from AIDS.

HIV infection and progression among women

HIV-uninfected women became infected at an age- and calendar-time-specific infection rate that further depended on pregnancy and breastfeeding status. Following infection, individuals entered into one of the four HIV disease stages according to observed proportions of infected persons who progress directly from primary infection to each stage. Untreated HIV progression occurred from one stage to the next: early asymptomatic stage without significant immunosuppression (CD4 ≥500) to late asymptomatic stage with mild immunosuppression (350 ≤ CD4 ≤499), to early AIDS with advanced immunosuppression (200 ≤ CD4 ≤349), and finally to full-blown AIDS with severe immunosuppression (CD4 < 200). HIV-infected women not on ART progressed from one CD4 cell count strata to the next at a rate that was reciprocal to the time expected to be spent in each CD4 strata. Women on ART were assumed to have a slower

progression rate compared to women who were not on ART. Women who dropped out of ART were assumed to progress to the next CD4 cell count stratum at the same rate as women who had never initiated ART.

Pregnancy and breastfeeding

Women became pregnant at age- and calendar-time-specific fertility rates that depended on women's HIV status, and ART status for HIV-infected women. The number of either pregnant or breastfeeding women at a particular time varied according to these fertility rates and the expected duration of pregnancy and breastfeeding. We assumed that women in both Option B and Option B+ breastfed their babies for the same fixed period of time.

ART uptake, retention and drop-out

ART uptake depended on ANC attendance rates (for either pregnant or breastfeeding women), ART eligibility under Malawi government guidelines in a given calendar year, and estimated ART uptake by eligible women. A small proportion of women could drop out of the ART program each year. According to common practice, and given a lack of empirical information about ART re-initiation according to disease stage, we assumed that drop-outs did not re-initiate ART unless they entered the final HIV stage (at which point they would be ill enough to hasten treatment re-initiation) or became pregnant and eligible for PMTCT. Once eligible for re-initiation, ART drop-outs re-initiated ART at the same rate that ART naïve persons initiated ART.

HIV transmission from women to men

The model specified a time-varying function (the net transmission rate) describing HIV transmission from women to men. Transmission was a function of the numbers of HIV-infected women in each model compartment at a given time, along with the relative infectiousness

associated with disease stage, ART status, and pregnancy status. Infectiousness among asymptomatic, not on ART, and not pregnant women served as the referent.

Model Analysis

All model analyses were done in R software, version 3.2.0. The differential equations were coded in deSolve,[132] a package in R that solves initial value problems (IVP) of ordinary differential equations (ODE), differential algebraic equations (DAE), partial differential equations (PDE) and delay differential equations (DeDE).

The model equations were specified in an R function describing the rate of change of the number of individuals in each compartment (state variables) as a function of input parameters and the time-varying numbers of individuals in the compartment. Input to the function included the initial values for the compartments, prior distributions on input parameters (transition rates), and the length of time for running the model.

The output from the system of differential equations was the number of women in each compartment over time. We used the output from the model to estimate and compare the net transmission rate for female-to-male transmission under Option B+ and Option B.

Model fitting

We used a Bayesian melding approach to fit our model to estimated ART coverage, estimated population-level HIV prevalence, and sentinel surveillance estimates of HIV prevalence from antenatal clinics in Lilongwe, Malawi. First, we ran 100,000 simulations using input parameter values sampled from the parameters' prior distributions, with each run resulting in a unique epidemic curve. Next, we filtered out curves in which output values for recent ART coverage and overall HIV prevalence were deemed implausible. The remaining curves were then assigned weights based on the likelihood of observing the ANC surveillance estimates for a given set of input parameters in our model. We then resampled (with replacement) the

epidemic curves, with the probability of resampling being proportional to the likelihood-based weight that was assigned to the curve. Finally, based on the resampled curves, we estimated the best posterior trajectory of the output (the median) with the corresponding 95% credible limits calculated as the lower 2.5th and the upper 97.5th percentiles of the output at each time point.

Comparing PMTCT strategies' impact on female-to-male transmission

After completing the Bayesian melding process, we ran three model scenarios to compare the effect of Option B+ with Option B on female-to-male transmission since Option B+ started (2011) and projected to 2020. In the first scenario, we assumed that Option B+ was the PMTCT strategy and used observed ART-for-PMTCT and ART-for-Health uptake up to 2014. From 2014 to 2020, we held the values of ART-for-PMTCT and ART-for-Health at the 2014 levels. In the second scenario, we assumed that Option B was the PMTCT strategy, with ART uptake values in the period 2011-2020 assumed to be the same as those assumed for Option B+; the only difference being ART discontinuation following breastfeeding cessation. In the third scenario, we also assumed that Option B was the PMTCT strategy, but we assumed that ART uptake values in the period 2011-2020 remained at 2011 levels; the differences in comparison to Option B+ were different ART uptake rates and ART discontinuation following breastfeeding cessation. In all three scenarios, all other parameters were fixed at 2011 values. We calculated the net transmission rate over time in each of the three scenarios and compared the Option B+ results to each of the Option B scenarios to assess the impact of Option B+ on heterosexual transmission between 2011 and 2020.

CHAPTER FOUR: THE RELATIONSHIP BETWEEN MATERNAL ANTIRETROVIRAL THERAPY INITIATION TIME AND PRETERM BIRTH: OPTION B+ FOR THE PREVENTION OF MOTHER-TO-CHILD HIV TRANSMISSION IN MALAWI

Introduction

Preterm birth, often defined as birth before 37 weeks of gestation,[27] is the second-leading cause of death in children under five years,[24] and accounts for 75% of all perinatal mortality worldwide.[25,26] Of the estimated 15 million infants born preterm in 2010, more than one million died as a result of prematurity.[24-27] In sub-Saharan Africa, about 12% of live births are preterm, with Malawi registering the highest preterm birth prevalence worldwide (18%).[23]

HIV is also endemic in sub-Saharan Africa, with 59% of all prevalent HIV infections occurring among women.[133] Prevention of mother-to-child HIV transmission (PMTCT) is thus a major public health priority. Antiretroviral therapy (ART) for HIV-infected women during pregnancy can virtually eliminate the risk of vertical HIV transmission,[1,4,134] with the additional, important benefit of reduced maternal morbidity and mortality.[9,135-137]

In July 2011, Malawi became the first country to adopt a strategy of universal life-long ART for pregnant and breastfeeding women regardless of HIV disease stage or CD4 count.[5] The scale-up of this approach, called “Option B+”, is expected to help bring an end to new pediatric HIV infections and substantially improve maternal health in settings with high HIV burdens.[101] Since the introduction of PMTCT Option B+ in Malawi, the number of pregnant or breastfeeding women on ART has increased dramatically,[6] and in 2013 the World Health Organization (WHO) recommended it for all countries with a generalized HIV epidemic.[8]

Despite the clear benefits of Option B+ for maternal health and the prevention of vertical HIV transmission, the effects of ART exposure during pregnancy on fetal development and birth outcomes are still unclear.[118-124] In particular, few studies have examined the relationship between the timing of maternal ART initiation and preterm delivery.[118,125,126] In this study, we used data from the maternity unit of a large, urban hospital in Malawi to estimate the risk of preterm births among HIV-infected women according to maternal ART status and time of ART initiation in the Option B+ era.

Methods

Study design, setting, and population

We conducted a retrospective cohort study using data collected at delivery from HIV-infected pregnant women delivering a singleton live birth at Bwaila Hospital in Lilongwe, Malawi from April 1, 2012 through November 15, 2015. The data for analysis were obtained from a point-of-care electronic medical record system (POC-EMRS) developed by Baobab Health Trust and hosted at the hospital. All records in the database of the POC-EMRS were entered directly by a health care worker while examining the mother at the time of delivery. Information about HIV status and ART (for HIV-infected women) was cross-checked with documentation in the mother's personal health passport, a government-issued document that contains information on general history, diagnoses, treatments, antenatal consultations, and deliveries.

ART duration during pregnancy is intrinsically linked to length of gestation (and thus preterm birth): women initiating ART later in pregnancy are necessarily closer to reaching term, and are therefore less likely to experience preterm birth. In an attempt to remove this potentially confounding relationship from our analysis, we constructed our study population such that the risk period for the outcome (preterm birth) was entirely separate from the eligible ART start times. Specifically, we restricted our analysis to women who: a) delivered on or after 27 weeks of gestation, and b) either started ART before 27 weeks or did not receive ART at all prior to

delivery (Figure 4.1). In other words, we chose a cut-off of 27 weeks to define the start of the risk period for preterm birth. This start point is at the upper end of values (which range from 20 to 28 weeks) that have been used in other settings;[27] this choice allowed us to minimize the number of women initiating ART during pregnancy that we would need to exclude in order to keep ART start times separate from the preterm risk period . Women with missing information on the main exposure (ART use) were also excluded.

This study was approved by the National Health Sciences Research Committee (NHSRC) of Malawi and the Institutional Review Board (IRB) at the University of North Carolina, Chapel Hill.

Variable definitions and classifications

HIV Status: Each woman's HIV status was determined at the time of admission to the maternity unit. Women whose health passports indicated prior HIV-positive test results were considered to be HIV-infected at the time of delivery; women without health passport documentation of HIV-positive status underwent HIV testing at the time of delivery to determine HIV infection status. Women found to be HIV-infected based on either the health passport or testing at delivery were recorded as such in the database and were eligible for inclusion in the study.

Main outcome – preterm birth: Preterm birth status was based on gestational age at delivery, which was calculated as the difference between date of delivery and the reported date of last menstrual period (LMP) recorded in the health passport during the first antenatal visit. We defined preterm birth as birth on or after 27 weeks of gestation and before 37 weeks of gestation. Births occurring at 37+ weeks of gestation were considered full term.[27]

Main exposure – ART: ART status and timing of ART initiation were determined at delivery according to maternal interview and information recorded in the health passport in the course of routine antenatal care. Eligible HIV-infected women with no history of ART use were

considered to be unexposed to ART for the purposes of this analysis, even if short-course ART was received at the time of delivery. These women comprised the "not on ART before delivery" group. Women whose health passports indicated ART initiation at or after 27 weeks of gestation were excluded from the analysis, as their ART exposure began after the start of the risk period for preterm birth. The remaining ART-exposed women were assigned to one of three categories according to timing of ART initiation: 1) before pregnancy (on ART at conception), 2) during the 1st trimester, or 3) during the 2nd trimester (specifically, the portion of the 2nd trimester <27 weeks).

Confounders

Using a directed acyclic graph (DAG)[138,139] containing variables in the database, we identified mother's education, age, and parity as potential confounders for inclusion in the analysis. Based on the functional form of the relationship between each confounder and outcome, we modeled mother's age as continuous and parity as ordinal. We used a manual, backward elimination, change-in-estimate strategy at a 10% retention threshold to assess the necessity of including each confounder in the final model.[140] We were unable to assess education as a confounder, as values for this variable were missing from 95% of records.

Statistical Analyses

We used Fisher exact tests to test differences in proportions between groups, and t-tests and one-way analysis of variance (ANOVA) to test differences in means as appropriate. We used log-binomial regression models to estimate unadjusted and adjusted risk ratios (uRRs and aRRs, respectively) and 95% confidence intervals (CI) of the association between ART exposure category and preterm birth, with those who did not initiate ART prior to delivery serving as the referent category.

In sub-analyses, we considered three preterm birth sub-categories: extremely to very preterm (27 to < 32 weeks), moderate preterm (32 to < 34 weeks), and late preterm (34 to <37 weeks).[27] In the first sub-analysis, we treated extremely to very preterm births (versus not preterm) as the outcome, excluding moderate to late preterm births from the analysis. In a second sub-analysis, we treated moderate to late preterm births (again versus not preterm) as the outcome, this time excluding extremely to very preterm births. In a third sub-analysis, we dichotomized the outcome as <34 weeks versus ≥34 weeks (extremely to moderate preterm vs. late preterm or full term), because births prior to 34 weeks' gestational age require advanced neonatal support, and their relationship with ART status and initiation time is thus of high clinical interest in this setting.

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC).

Results

Among 66,029 women who delivered in the maternity ward at Bwaila Hospital during the study period, 6,853 women (10.4%) were known to be HIV-infected. Of the HIV-infected women, 4,988 (72.8%) had singleton live births at 27+ weeks of gestation and were thus eligible for our study. After excluding women with missing ART initiation time and those who initiated ART at or after 27 weeks, 3,074 women were included in the analyses (Figure 4.2). Most women had initiated ART before pregnancy (N=1139, 37.0%) or during the second trimester (N=1503, 48.9%). Only 5.4% had not initiated ART prior to delivery (N=165), including three women who received ART at the time of delivery only.

On average, women who had never initiated ART prior to delivery were younger than those who had received ART during pregnancy, and age at delivery increased with earlier ART initiation times ($p < 0.001$) (Table 4.1). The distribution of parity was different across the ART exposure categories ($p < 0.001$), and mean gestational age at delivery was similar between

those who never initiated ART and those who were on ART, regardless of the time of ART initiation (p = 0.05) (Table 4.1). A total of 731 preterm births were observed during the study period (risk = 24%; 95% CI: 22% - 25%).Women who delivered preterm babies were on average younger than those who delivered full term babies (mean age = 27.6 vs 28.4, p < 0.001) (Table 4.1).

In the main analysis, the risk of preterm birth was similar in women who had initiated ART at any point prior to delivery compared to those who never initiated ART (aRR = 0.88; 95% CI: 0.65 – 1.19) (Table 4.2). There was not a clear trend in the relationship between timing of ART initiation and risk of preterm birth. Compared to women who had not initiated ART prior to delivery, the aRRs for preterm birth were 0.78 (95% CI: 0.57 – 1.08), 1.03 (95% CI: 0.72 – 1.49), and 0.92 (95% CI: 0.67 – 1.25) for initiating ART before pregnancy, during the 1st trimester, and during the 2nd trimester, respectively, after adjustment for mother's age and parity.

In sub-analyses focusing on extremely to very preterm birth vs. full term birth, we found ART initiation at any point before delivery to be strongly protective (aRR = 0.43; 95% CI: 0.26 – 0.72) (Table 4.3). Separate consideration of ART initiation before pregnancy (aRR = 0.42; 95% CI: 0.24 – 0.73), in the 1st trimester (aRR = 0.54; 95%CI: 0.27 – 1.10), and in the 2nd trimester (aRR = 0.42; 95% CI: 0.24 – 0.72) suggested that all three initiation times were protective against extremely to very preterm birth.

There was some evidence of an increased risk of moderate to late preterm (vs. full term) births associated with ART use prior to delivery (aRR = 1.16; 95% CI: 0.75 – 1.80) (Table 3). In particular, initiation in the 1st or 2nd trimester (vs. no ART before delivery) was associated with higher risk of moderate to late preterm birth, but these estimates were imprecise. ART initiation prior to pregnancy was not associated with moderate to late preterm birth.

Finally, we found ART use prior to delivery to be suggestive of a protective effect against birth at less than 34 weeks' gestation overall (aRR = 0.70; 95% CI: 0.42 – 1.17) (Table 3). The

point estimates for each of the three start times (before pregnancy, during the 1st trimester, during the 2nd trimester) were also suggestive of protective effects against birth prior to 34 weeks.

Discussion

In this study of birth outcomes among infants born to HIV-infected mothers in Malawi since the start of Option B+, we did not find a strong association between ART initiation prior to delivery and preterm birth overall. Importantly, though, we found ART prior to delivery to be quite strongly associated with a reduced risk of extremely to very preterm birth (birth between 27 and 32 weeks of gestation), and moderately associated with a reduction in preterm birth prior to 34 weeks. These results are encouraging because mortality increases as gestational age decreases, with only 30% of babies born between 28 and 32 weeks in low-income countries surviving.[27] In general, ART initiation prior to conception was associated with better outcomes relative to non-use of ART than was initiation during pregnancy. Taken together, these findings suggest that ART during pregnancy does not increase the risk of preterm birth, and that it may in fact be protective against severe adverse birth outcomes.

Our findings are consistent with the results of previous studies that have shown a protective effect of earlier maternal ART against preterm birth. A study of predominantly black African pregnant women who delivered at a single hospital in London found a decreased odds of preterm delivery among women who conceived while receiving ART compared to women who received ART following conception.[141] Results from a study in Malawi and Mozambique showed a protective effect of a longer course of ART during pregnancy against preterm birth, although the investigators did not differentiate between those who started ART prior to conception and those who started during pregnancy.[142]

A small number of previous studies in both developed and developing countries have found early ART exposure during pregnancy to be associated with increased risk of preterm

birth. In an analysis from abstracted obstetrical records at six sites in Botswana, women who started highly active antiretroviral therapy (HAART) prior to pregnancy had a higher odds of delivering preterm babies compared to HIV-infected women with no ART exposure and those initiating HAART or zidovudine monotherapy during pregnancy.[120] Similarly, results from a prospective cohort study in Brazil found that starting ART before conception increased the odds of preterm birth, although the effect estimate was very imprecise.[125] Importantly, both of these studies were performed in the era when ART initiation for health and PMTCT was only available to those with advanced disease. Advanced maternal HIV is associated with increased risk of preterm birth[143] and these earlier findings may not be directly applicable to the PMTCT Option B+ era when lifelong ART is initiated during pregnancy regardless of HIV disease stage or CD4 count.

To our knowledge, our study is the first to provide evidence that ART initiation prior to conception is protective against preterm birth in the era of PMTCT Option B+. As the Option B+ program matures and the proportion of women on lifelong ART following a prior pregnancy grows, we expect that an increasing proportion of women will be on ART prior to conception. Our finding that the risk of preterm was lowest in this group suggests that preterm prevalence among HIV-infected mothers is likely to decrease as the time since Option B+ implementation increases. Our results also suggest that being on ART during pregnancy is protective against extremely to very preterm birth, regardless of time of ART initiation. These findings suggest that increased ART uptake in the Option B+ era could have a profound impact on preterm birth and neonatal mortality in developing countries where fertility rates are high, HIV is endemic, and advanced nursery facilities are not readily available.

Several mechanisms have been hypothesized for possible adverse effects of ART on birth outcomes. Specifically, it has been proposed that protease inhibitor (PI)-based ART could induce preterm birth by a cytokine-mediated regulation of the immune system through increased Th1 and decreased Th2 cytokines production.[144,145] Women with recurrent pregnancy losses

have been observed to have increased Th1 and decreased Th2 cytokines.[146,147] Compared to non-PI-based ART, women on PI-based ART have a higher risk of having preterm birth.[120,121] However, the same cytokine mechanism has been hypothesized to be protective against HIV disease progression.[148,149] Women who are on established ART before conception may have a stabilized cytokine environment due to long exposure to ART, which can be one reason we observed ART initiation prior to pregnancy being protective against preterm birth. Additionally, the ART regimen used in Malawi, tenofovir / lamivudine / efavirenz (TDF/3TC/EFV), is not PI-based, which may explain the similar risk of preterm birth we observed in women who initiated ART at any point prior to 27 weeks and those who never initiated ART.

Studies focusing on the association between duration of ART exposure *in utero* and other fetal outcomes have also suggested that the benefits of earlier ART outweigh the risks. Earlier ART initiation during pregnancy was not associated with increased risk of stillbirth or low birthweight (LBW) in South Africa (with ART initiation dichotomized at < 28 weeks or ≥ 28 weeks of pregnancy),[118] or with LBW in United States (with ART initiation dichotomized at ≤ 25 weeks or ≥ 32 weeks of gestation).[124] A recent cohort analysis in Zambia among infants born at term also did not find increased risk of LBW or decreased mean birthweight due to longer duration of ART during pregnancy.[150]

ART duration during pregnancy is intrinsically linked to length of gestation and thus preterm birth. To confine the preterm risk period to an interval in which women were either always or never on ART, and to maximize the number of ART initiation intervals (before pregnancy, during the 1st trimester, during the 2nd trimester) prior to the start of the risk period that we could examine, we restricted our analysis to births that occurred on or after 27 weeks and to women who either started ART before 27 weeks or did not receive ART at all prior to delivery. We are therefore unable to draw any conclusions about the effects of early ART on extremely early preterm birth (prior to 27 weeks) or the effects of ART initiated at or after 27 weeks on subsequent preterm births.

We also note that there may have been some misclassification of preterm status and ART initiation time within pregnancy due to inaccurate estimates of the last menstrual period. The general consistency of our findings across ART initiation times suggests that such misclassification may not be a large concern in our analyses, and our specific finding that women initiating ART at any point during pregnancy were less likely to experience extremely to very preterm birth (vs. term birth) may be especially robust, given the five-week difference between the upper gestational age limit of very preterm (32 weeks) and the lower limit of full term (37 weeks).

Information on several potential confounders was either unavailable or insufficient for inclusion in analyses. In particular, we did not have information on the interrelated covariates of ART adherence, CD4 count, and viral load. Poor ART adherence can result in drug resistance,[151,152] lower CD4, and higher viral loads, leading to adverse maternal and birth outcomes. In general, ART adherence is high during pregnancy,[153] and we expect that the fixed-dose TDF/3TC/EFV combination of one tablet per day in our study population would have encouraged high adherence in all women receiving ART.[5] Furthermore, we would consider viral load and CD4 count to be casual intermediates between ART and preterm birth, and thus statistical adjustment would have been inappropriate even if viral load and CD4 data had been available. We also note that there may have been data entry errors and incomplete data entry, but we do not expect such errors or incompleteness to have been differential according to exposure or outcome status.

ART initiation in pregnancy is an indicator of access to prenatal care and other health care services. In Malawi, HIV-infected women not on ART are initiated on life-long ART during an antenatal care visit,[154] in addition to receiving standard prenatal care. Women who attend antenatal care are less likely to deliver low birthweight infants, especially from preterm births.[155,156] In the likely event that the women who had never initiated ART prior to delivery were less likely to have had access to prenatal care, then the higher risk of preterm births among

those who did not initiate ART may not be fully attributable to lack of ART during pregnancy. No information on dates or numbers of antenatal visits was available in the POC-EMRS to allow control for antenatal care receipt in our analyses.

Nevertheless, our results suggest that the risk of preterm birth – particularly early preterm birth – is low among women initiating ART prior to delivery, especially among those who initiate ART prior to conception. As the era of PMTCT Option B+ continues, post-weaning retention on therapy of women who initiate ART during pregnancy should thus be a priority. Additionally, these findings suggest that HIV testing of women who wish to become pregnant, followed by ART initiation prior to conception in those testing HIV-positive, could be beneficial. If adequate uptake and retention can be achieved, then PMTCT Option B+ may not only dramatically reduce vertical HIV transmission and improve maternal health, but also reduce preterm birth in settings with heavy, overlapping burdens of HIV and neonatal mortality.

Tables and Figures

Table 4.1. Characteristics of Study Population

Characteristics	Birth Status		ART initiation time during pregnancy			
	Preterm N (%) 731 (23.8)	Full Term N %) 2343 (76.2)	Before pregnancy N (%) 1139 (37.0%)	1st trimester N (%) 267 (8.7%)	2nd trimester* N (%) 1503 (48.9%)	Never initiated N (%) 165 (5.4%)
Mother's age (mean, SD)	27.6 (5.6)	28.4 (5.8)	30.4 (5.4)	27.2 (5.4)	26.9 (5.5)	25.6 (5.5)
Gestation weeks at delivery (mean, SD)	34.0 (2.2)	39.4 (1.3)	38.3 (2.7)	37.9 (2.9)	38.1 (2.8)	38.0 (3,3)
Parity						
Nulliparity	20 (3.3)	46 (2.3)	12 (1.1)	9 (4.1)	40 (3.4)	5 (4.1)
Primiparity (1 child)	163 (26.9)	567 (28.6)	239 (22.3)	64 (29.2)	384 (32.7)	43 (35.5)
Low Multiparity (2–4 children)	394 (65.0)	1243 (62.8)	739 (68.9)	140 (63.9)	695 (59.2)	63 (52.1)
Grand Multiparity (≥ 5 children)	29 (4.8)	124 (6.3)	82 (7.7)	6 (2.7)	55 (6.7)	10 (8.3)

* before 27 weeks

Table 4.2. Associations between ART status and timing of initiation with preterm birth

ART Initiation Status	Preterm N (%) 731 (23.8)	Full Term N (%) 2343 (76.2)	Unadjusted RR (95% CI)	Adjusted RR† (95% CI)
On ART	690 (94.4)	2219 (94.7)	0.95 (0.73, 1.25)	0.88 (0.65, 1.19)
Never Initiated ART	41 (5.6)	124 (5.3)	1.00	1.00
Before Pregnancy	235 (32.2)	904 (38.6)	0.83 (0.62, 1.11)	0.78 (0.57, 1.08)
1st Trimester	77 (10.5)	190 (8.1)	1.16 (0.84, 1.61)	1.03 (0.72, 1.49)
2nd Trimester*	378 (51.7)	1125 (48.0)	1.01 (0.77, 1.34)	0.92 (0.67, 1.25)
Never Initiated	41 (5.6)	124 (5.3)	1.00	1.00

†Adjusted for mother's age and parity

* before 27 weeks

Table 4.3. Associations between ART status and timing of initiation with alternate preterm categorizations

ART Initiation status	Extremely to Very Preterm* N (%)	Full Term‡ N (%)	Unadjusted RR (95% CI)	Adjusted RR§ (95% CI)
	149 (6.0)	2343 (94)		
On ART	133 (86.3)	2219 (94.7)	0.49 (0.30, 0.81)	0.43 (0.26, 0.72)
Never Initiated	16 (10.7)	124 (5.3)	1.00	1.00
Before Pregnancy	50 (33.6)	904 (38.6)	0.46 (0.27, 0.78)	0.42 (0.24, 0.73)
1st Trimester	14 (9.4)	190 (8.1)	0.60 (0.30, 1.19)	0.54 (0.27, 1.10)
2nd Trimester**	69 (46.3)	1125 (48.0)	0.51 (0.30, 0.85)	0.42 (0.24, 0.72)
Never Initiated	16 (10.7)	124 (5.3)	1.00	1.00
	Moderate to late Preterm† N (%)	Full Term N (%)		
	582 (19.9)	2343 (81.1)		
On ART	557 (95.7)	2219 (94.7)	1.20 (0.83, 1.72)	1.16 (0.75, 1.80)
Never Initiated	25 (4.3)	124 (5.3)	1.00	1.00
Before Pregnancy	185 (31.8)	904 (38.6)	1.01 (0.69, 1.48)	1.01 (0.64, 1.11)
1st Trimester	63 (10.8)	190 (8.1)	1.48 (0.98, 2.25)	1.37 (0.83, 2.25)
2nd Trimester**	309 (53.1)	1125 (48.0)	1.28 (0.89, 1.86)	1.24 (0.79, 1.93)
Never Initiated	25 (4.3)	124 (5.3)	1.00	1.00

Table 4.3. Associations between ART status and timing of initiation with alternate preterm categorizations (continued)

ART Initiation Status	< 34 weeks N (%) 243 (7.9)	≥ 34 weeks N (%) 2831 (92.1)	Unadjusted RR (95% CI)	Adjusted RR[§] (95% CI)
On ART	243 (93.4)	2682 (94.7)	0.80 (0.50, 1.30)	0.70 (0.42, 1.17)
Never Initiated	16 (6.6)	149 (5.3)	1.00	1.00
Before Pregnancy	83 (34.2)	1056 (37.3)	0.75 (0.45, 1.25)	0.68 (0.40, 1.17)
1st Trimester	24 (9.8)	243 (8.6)	0.93 (0.51, 1.69)	0.85 (0.45, 1.58)
2nd Trimester**	120 (49.4)	1383 (48.9)	0.82 (0.50, 1.35)	0.69 (0.41, 1.17)
Never Initiated	16 (6.6)	149 (5.3)	1.00	1.00

[*] Extremely to very preterm: 27 to < 32 gestation weeks

[†] Moderate to late preterm: 32 to < 37 gestation weeks

[‡] Full term: ≥ 37 gestation weeks

[§] Adjusted for mother's age and parity

** before 27 weeks

Figure 4.1. Study eligibility on the basis of maternal ART start time and gestational age at birth

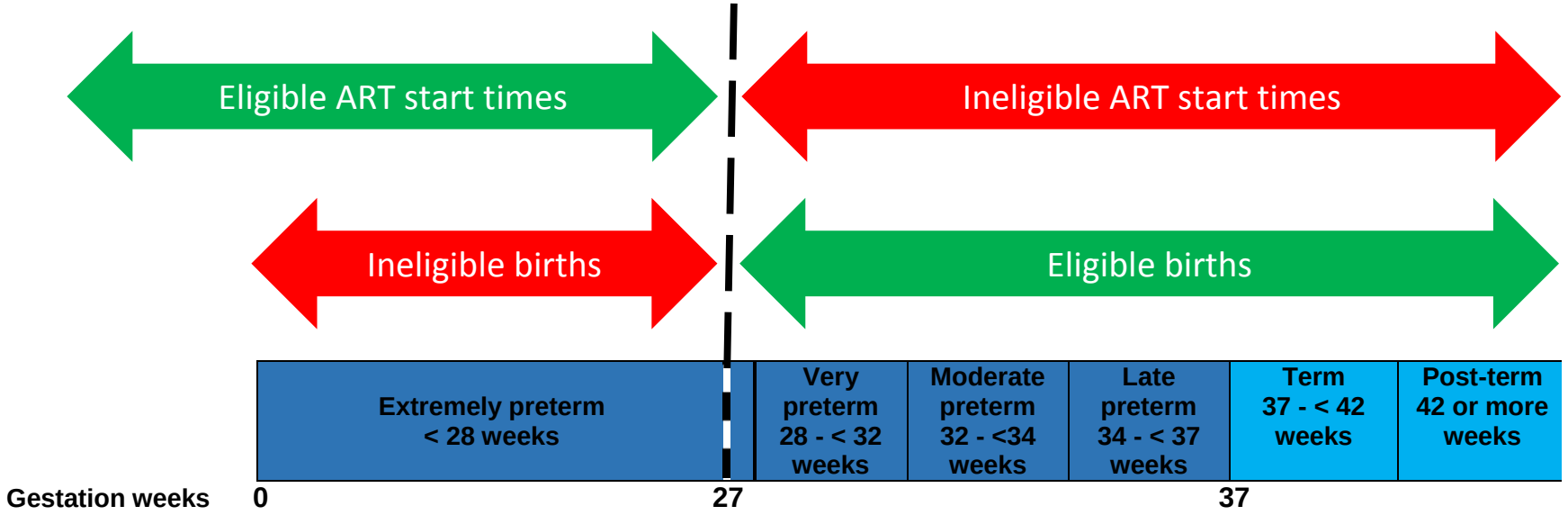
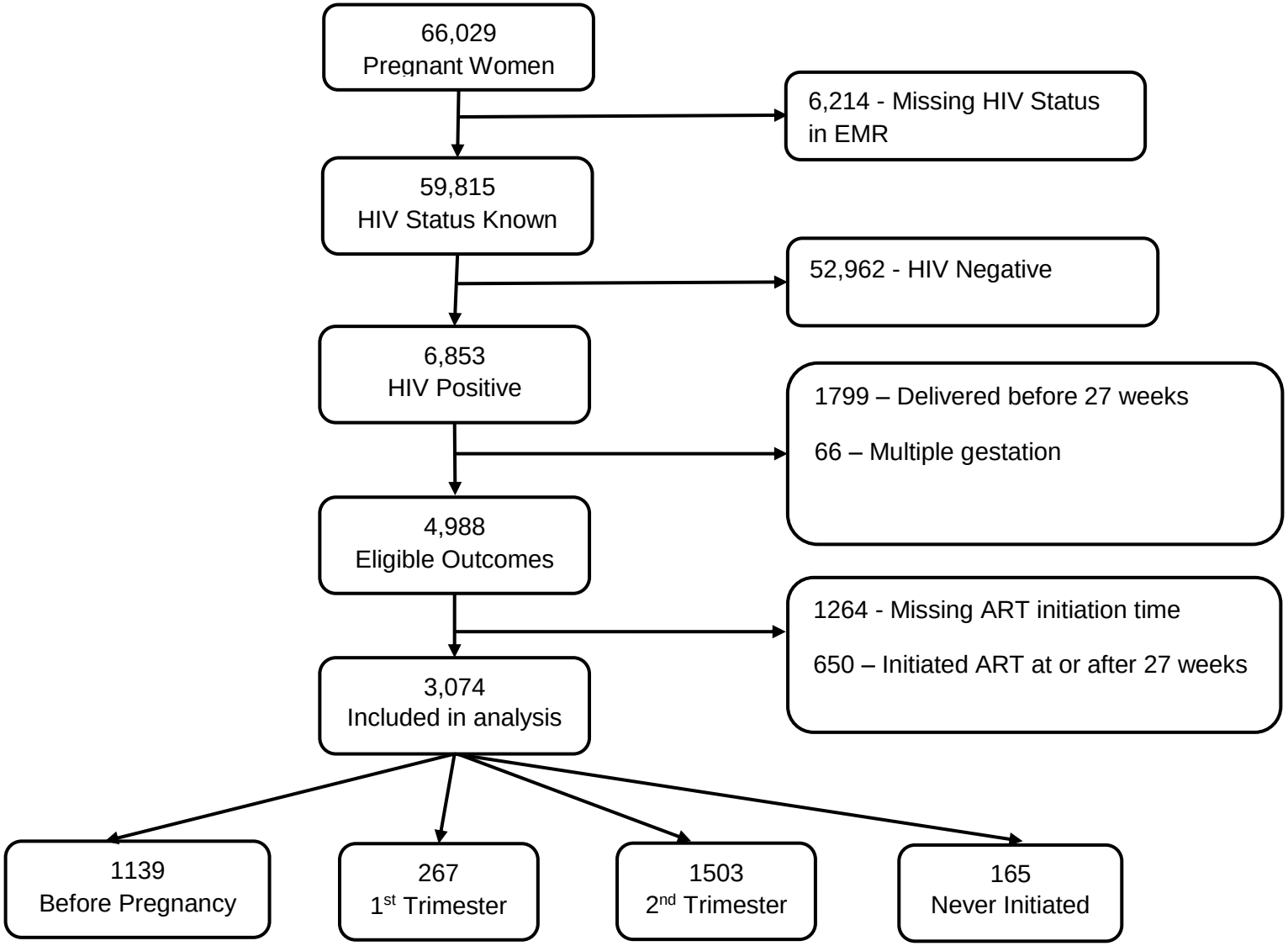


Figure 4.2 Flow diagram of the inclusion criteria for the women included in the analysis



CHAPTER FIVE: THE POPULATION-LEVEL EFFECT OF OPTION B+ ON FEMALE-TO-MALE HIV TRANSMISSION IN MALAWI: A MATHEMATICAL MODELING ANALYSIS

Introduction

In 2013, an estimated 1.5 million people were newly infected with HIV in sub-Saharan Africa, mostly through heterosexual transmission.[12] High serum viral load in HIV-infected persons increases the risk of transmitting the virus to their sexual partners.[106] When treated with antiretroviral therapy (ART), HIV-infected persons have reduced concentrations of HIV viral load in their plasma,[107,108] semen,[109,110] and cervicovaginal fluid.[108] The ability of ART to reduce HIV viral loads has been pivotal in preventing mother-to-child transmission (MTCT),[97,111] and reducing HIV transmission among adults.[112-114]

Worldwide, efforts have been made to increase ART availability to all HIV-infected pregnant and breastfeeding women. The recommendations and guidelines in the implementation of prevention of mother-to-child transmission (PMTCT) programs have been revised over time as simplified, standardized, and more potent ART regimens have become available.[98-102] In 2010, the World Health Organization (WHO) issued guidelines for PMTCT that included two approaches: Option A and Option B. Both Options A and B include lifelong, triple ART for HIV-infected pregnant women with CD4 cell count ≤ 350 cells per mm^3. Under Option A, women with CD4 > 350 cells per mm^3 start azidothymidine (AZT) as early as 14 weeks of gestation, followed during labor by single dose nevirapine (sdNVP) plus the first dose of azidothymidine / lamivudine (AZT/3TC), and then daily AZT/3TC through the first seven postpartum days. Under Option B, women with CD4 > 350 cells per mm^3 start triple ART as early as 14 weeks of gestation and continue up to one week after breastfeeding cessation.

Limited access to CD4 cell count analysis in developing countries has been a barrier to rapid expansion of PMTCT programs using Option A and Option B, as both strategies differentiate treatment regimens according to CD4 count. In 2011, the Malawi government proposed and started implementing a new and simplified approach to PMTCT called Option B+,[5] now adopted by WHO for all countries with generalized HIV epidemics.[8] Under Option B+, all confirmed HIV-infected pregnant or breastfeeding women are started on lifelong ART regardless of CD4 cell count. Besides preventing MTCT, the Option B+ approach has other potential ancillary public health benefits beyond those offered by Option A and Option B, especially continued prevention of sexual HIV transmission from HIV-infected women beyond pregnancy and breastfeeding.[5,102]

Programmatic efficiency of Option B+ over Option B has been shown in Malawi through a dramatic increase in the number of pregnant or breastfeeding women on ART.[6] However, the impact of Option B+ on the adult HIV / AIDS burden through reduced heterosexual transmission has not been quantified in this setting. In this study, we developed a mathematical model to estimate the expected relative reduction in HIV incidence among men in Lilongwe, Malawi under Option B+ versus Option B from 2011 to 2020.

Methods

Mathematical model specification

We developed a deterministic, compartmental model to study the effect of Option B+ on heterosexual HIV transmission from women to men. The model captures the population dynamics of women only (Figure 5.1), stratified into compartments by HIV status as HIV-uninfected (susceptible; S) and HIV-infected (I), age cohorts (15-19, 20-24, 25-34 and 35-49), and pregnancy / breastfeeding status (either pregnant or breastfeeding, neither pregnant nor breastfeeding). HIV-infected women are further stratified by HIV disease stage (CD4 ≥500, 350

≤ CD4 ≤499, 200 ≤ CD4 ≤349, and CD4 < 200) and ART status (ART naïve, on ART, and ART drop-outs).

Young women enter the model population in the non-pregnant, HIV-susceptible, 15-19 years age group and then age into older age groups at rates reciprocal to the expected time to be spent in each age category. Following modeling convention, both HIV-uninfected and HIV-infected persons are removed from the population by aging out of the sexually active population upon reaching 50 years of age. The initial size of the model population was based on census estimates for Lilongwe, Malawi.[130] Model processes are described below, with corresponding parameter values in Tables 5.1 and 5.2. Additional details on the modeling approach are provided in the supplemental material.

HIV infection in women

HIV-susceptible women become infected at an age- and calendar-time-specific incidence rate [157,158] that also depends on pregnant/breastfeeding status (Table 5.1).[159] At the time of infection, women enter one of four HIV disease stages according to proportions estimated in the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort of infected persons who progress directly from primary infection to each stage:[160] early asymptomatic stage without significant immunosuppression (CD4 ≥500), late asymptomatic stage with mild immunosuppression (350 ≤ CD4 ≤499), early AIDS with advanced immunosuppression (200 ≤ CD4 ≤349), and full-blown AIDS with severe immunosuppression (CD4 < 200). Untreated HIV progression from one stage to the next occurs at a constant rate, as does death due to AIDS in the final stage.[160]

ART uptake, retention, and effects on HIV progression

ART eligibility for both either pregnant or breastfeeding women and neither pregnant nor breastfeeding varies over time according to Malawi Government guidelines in the years since

ART became available (Table 2).[154,161-163] Since ART-for-health eligibility criterion for years 2000 – 2010 was CD4 < 250 and not CD4 < 200 in Malawi, we allowed some women with 200 ≤ CD4 ≤ 349 to initiate ART during this period. Among ART-eligible women, ART initiation depends (for pregnant women) on ANC uptake [131,164-166] and (for both pregnant and not-pregnant women) observed ART uptake rates for PMTCT and health, respectively.[167-169] Women drop out of treatment at a constant rate, with assumed values for this rate based on estimates used in previous mathematical modeling studies;[170-177] these women are assumed not to re-initiate ART until their CD4 cell count falls to < 200 or they become eligible for PMTCT via pregnancy. Women also discontinue ART after weaning under the Option B scenario if their CD4 is above contemporary ART eligibility thresholds (see *Comparison of Option B+ vs. Option B impact on female-to-male HIV transmission* below). Once women meet re-initiation criteria (i.e., pregnancy or CD4 < 200), ART re-initiation is assumed to occur at the same rate as initial ART uptake among ART-naïve persons.

Women on ART are assumed to have a long period of "effective ART" during which their CD4 cell count remains within the category in which they initiated ART, and their progression rate is assumed to be much slower compared to women not on ART.[170,171,178] Women who drop out of ART are assumed to progress to the next CD4 cell count stratum at the same rate as ART-naïve women.

Pregnancy and breastfeeding

Women become pregnant at age- and calendar-time-specific fertility rates[179] that further depend on HIV status[180,181] and (for HIV-infected women) ART status.[104] Women exit the pregnant / breastfeeding compartments at a constant rate based on the mean expected duration of pregnancy and breastfeeding, with mean breastfeeding duration varying over time according to DHS estimates.[131,164-166]

HIV transmission from women to men

Following Bezemer et al [182] and van Sighem et al,[183] HIV incidence in men is described by a time-varying *net transmission rate*, which specifies transmission as a function of the numbers of HIV-infected women in each compartment and the relative infectiousness associated with each compartment. More specifically, in our model, the net transmission rate from women to men is a function of the numbers and relative infectiousness of HIV-infected women according to disease stage, ART status, and pregnancy status. Asymptomatic women who are not on ART and not pregnant serve as the referent, with later disease stages and pregnancy resulting in higher infectiousness,[184,185] and ART use resulting in decreased infectiousness.[114,184,186]

Model analysis

All analyses were performed using R software, version 3.2.0. The model code was formulated in a set of ordinary differential equations implemented in the R software package deSolve.[132]

Model fitting

We used a Bayesian melding approach[187-190] to fit our model to empirical data on HIV prevalence and ART uptake. In brief, we first ran 100,000 model simulations, with input parameter values drawn in each independent run from the prior distributions given in Tables 5.1 and 5.2. Next, we filtered out simulations in which output values for recent ART coverage and overall HIV prevalence were deemed implausible. More detail is available in the supplemental material, but briefly, we required that HIV prevalence among all women was consistent with 2004 and 2010 DHS estimates for female HIV prevalence in urban settings in Malawi (as Lilongwe-specific estimates were unavailable),[131,166] and that ART coverage for health and PMTCT was consistent with UNAIDS estimates in the period 2008-2010.[191] Following this

filtering process, we assigned each surviving simulation a weight based on the likelihood of empirical HIV prevalence among pregnant women from ANC surveillance in Lilongwe (1987-2007), given the input parameter values in the simulation. Finally, we resampled (with replacement) from the simulations, with probability of selection proportional to the assigned weight. From the resampled runs we then calculated median values, along with 95% credible limits from the 2.5th and 97.5th percentile values, for model inputs and outputs.

Comparison of Option B+ vs. Option B impact on female-to-male HIV transmission

To estimate the projected impact of Option B+ on female-to-male transmission over the strategy's first nine years of existence in Lilongwe, we ran three model scenarios from 2011 through 2020: 1) one in which we assumed that Option B+ was the PMTCT strategy, with ART-for-PMTCT uptake set to observed values[168] in the period 2011-2014 and then fixed at the 2014 value for the period 2014-2020; 2) one in which we assumed that Option B was the PMTCT strategy, with ART uptake values in the period 2011-2020 assumed to be the same as those assumed for Option B+; and 3) one in which we assumed that Option B was the PMTCT strategy, but with ART uptake values in the period 2011-2020 assumed to remain at 2011 levels. In all three scenarios, all other parameters were fixed at 2011 values. Thus, the key difference between Scenario 2 and Scenario 1 is the difference in ART discontinuation following breastfeeding cessation: Under Scenario 2 (Option B), women with CD4 above the national ART-for-health eligibility criterion (i.e., 350 in the period 2011-2014 and 500 in the period 2014-2020) discontinued ART upon leaving the pregnant/breastfeeding compartment, but all women stayed on ART in Scenario 1 (Option B+). This difference also held in the comparison of Scenario 3 and Scenario 1, with the additional difference of increasing ART uptake associated with the lack of a CD4 testing requirement under Option B+ but not Option B. More specifically, uptake of ART for PMTCT was assumed to increase between 2011 and 2014 in the Option B+ scenario (Scenario 1) but not in the Option B scenario (Scenario 3).

We used results from the three simulations to estimate the net transmission rate under each strategy each year. We then compared the net transmission rate under Option B+ and Option B in two sets of comparisons: Scenario 2 vs. Scenario 1 and Scenario 3 vs. Scenario 1. In these comparisons, we derived the relative HIV incidence reduction in men due to PMTCT Option B+ at each time point by dividing the net transmission rate from women under Option B+ (Scenario 1) by the corresponding net transmission rate under each of the Option B scenarios (Scenarios 2 and 3) separately.

Results

The Bayesian melding procedure produced 12,000 unique HIV prevalence curves among pregnant/breastfeeding women that were in good agreement with the empirical HIV prevalence data from ANC surveillance in Lilongwe (Figure 5.2). Using the median from the simulations, we estimated that the HIV prevalence among pregnant women peaked in 1998, (23.6%; 95% credible intervals (CI): 19.9 – 27.6), dropped to 17.9% (95% CI: 15.6 – 20.3) in 2008, and then to 15.1% (95% CI: 13.0 – 17.4) in 2011. The corresponding HIV prevalence in the overall female population in 2004 and 2010 was 21.2% (95% CI: 18.9 – 22.4) and 17.4% (95% CI: 15.5– 19.0) (results not shown), which are within the range of DHS estimates of 2004 and 2010 among women for Malawi urban areas, respectively.

Estimated female-to-male HIV transmission from 2011 through 2020 was lower assuming Option B+ than assuming Option B under both sets of Option B scenarios (Figure 5.3). Comparing Option B+ to the Option B scenario in which ART uptake values in the period 2011-2020 were assumed to be the same as those assumed for Option B+ (i.e., in the comparison of Scenario 2 to Scenario 1), the estimated relative HIV incidence (RI) under Option B+ was 4% lower (median RI = 0.96; 95% CI: 0.94 – 0.97) in 2015 and was projected to be 7% lower (median RI = 0.93; 95% CI: 0.90 – 0.95) by 2020. Comparing Option B+ to the Option B scenario in which ART uptake values in the period 2011-2020 were assumed to remain at 2011

levels (i.e., the comparison of Scenario 3 to Scenario 1), the estimated RI under Option B+ was 14% lower (median RI = 0.86; 95% CI: 0.84 – 0.88) in 2015 and was projected to be 21% lower (median RI = 0.79; 95% CI: 0.74 – 0.83) by 2020.

Model-predicted ART coverage among not-pregnant/not-breastfeeding women increased from 40% (95% CI: 34 - 47) of treatment-eligible women in 2011 to 85% (95% CI: 78 - 92), 78% (95% CI: 72 - 84), and 71% (95% CI: 64 - 77) in 2020 under scenarios 1, 2, and 3, respectively (results not shown). Estimated ART coverage among pregnant/breastfeeding women increased from 22% (95% CI: 18 - 26) in 2011 to 78% (95% CI: 73 - 82), 76% (95% CI: 72 - 80), and 68% (95% CI: 63 - 73) in 2020 under the three scenarios.

Discussion

Our mathematical modeling study provides the first quantitative estimates of HIV incidence reductions associated with Option B+ in Malawi, the first country to implement this PMTCT strategy at a national level. Our results suggest that the Option B+ strategy has considerable potential to reduce female-to-male HIV transmission in addition to its benefits for preventing vertical transmission. The incidence reductions that we observed were particularly notable when we assumed that Option B+ affected not only the duration of therapy (by calling for lifelong treatment even after breastfeeding cessation), but also the proportion of pregnant women initiating ART to begin with (by removing CD4 testing barriers). As reflected in our model, national treatment guidelines recently increased the CD4 threshold for ART-for-health from 350 to 500, such that more women in the “Option B” scenario now remain eligible for ART after breastfeeding cessation than was the case prior to 2014. This higher CD4 threshold results in a smaller difference in ART duration under Option B+ vs. Option B, such that increased ART uptake due to removal of CD4 testing barriers may be an important and underappreciated mechanism for Option B+ to reduce heterosexual transmission in this region.

In sub-Saharan Africa, the need for PMTCT remains high and is likely to increase. A large number of new and prevalent HIV infections in the region are among reproductive-aged women.[55] The rapid expansion of ART in this region should continue to result in growing proportions of women receiving ART, and ART-induced rebounds from HIV-related sub-fertility[103-105] will likely result in increased proportions of HIV-infected women in antenatal clinic populations. ART adherence support in these settings could help to ensure that the benefits of ART – both for PMTCT and for the prevention of heterosexual transmission – can be realized in the Option B+ era.

Our estimated incidence reductions are relatively consistent with – but somewhat lower than – the results of the single previous mathematical modeling study that estimated the impact of different PMTCT strategies on heterosexual transmission.[192] In the application of this earlier model to four separate settings (Kenya, Zambia, South Africa, and Vietnam), Option B+ was estimated to avert 18% (in Kenya) to 115% (in South Africa) more heterosexual transmissions than Option B with a CD4 eligibility threshold of 350 for ART for health, and 17% – 61 % more infections than Option B when the CD4 threshold was 500. In our comparison of Option B+ vs. Option B, the ART-for-health CD4 threshold was 350 from 2011 through 2013, and 500 from 2014 through 2020. As such, the reductions of 17% - 61% obtained for the CD4 threshold of 500 in the prior study – particularly estimates of 17% in Kenya and 25% in Zambia – are most relevant to our own. We note that our estimated reductions of 7% (5%-10%) and 21% (17%-26%) in 2020 relate to a period of only nine years (2011-2020), whereas the estimated benefits of Option B+ in the earlier modeling study were accrued over a 35-year period, potentially explaining the lower estimates that we obtained.

Mathematical models have also been used to evaluate the benefits of Option B and Option B+ in terms of mother-to-child transmission, infant and maternal health, and cost-effectiveness. In a model based largely on parameters calculated from programmatic data in Malawi, Option B+ resulted in less MTCT and more women already on ART during their second

pregnancy than under Option B.[193] Greater reductions in MTCT using Option B+ were also reported in a model focusing on Kenya, Zambia, South Africa and Vietnam.[192] A model based on data from Zimbabwe showed increased life expectancy among infants and their mothers under Option B+ vs. Option B.[194] In each of these models, Option B+ was found to be more cost-effective than Option B in all sub-Saharan African countries except South Africa.

Our model incorporated numerous details underlying demographic and transmission dynamics, including age stratification, time-varying parameter values, and the effects of HIV and ART on survival, fertility, and infectiousness. We based our model parameters largely on Malawi-specific sources, including DHS reports, UNAIDS estimates, and local programmatic data. Our Bayesian melding approach allowed us to accurately reproduce HIV prevalence trends in this setting – both in ANC populations and the general female population overall – along with trends in ART coverage. This model fitting procedure also allowed us to account for uncertainty in input parameters and express uncertainty (in the form of credible limits) around our model outputs.

Mathematical modeling results depend on simplifying assumptions that are necessary for the development of tractable models. In our case, we only considered incidence reductions from women to men, without taking into account the subsequent reductions in incidence that would occur among women as a result of reduced HIV prevalence in men, which would then result in further incidence reductions in men, and so on. The omission of these non-linear feedback loops will necessarily result in underestimation of overall incidence reductions attributable to Option B+; however, we attempted to minimize this underestimation by limiting our time horizon to a relatively short period of nine years. We also note that we did not consider acute HIV infection and its attendant increased infectiousness in our model. We deliberately chose this simplification because recognition of and treatment during acute HIV is rare in this region. Because neither Option B nor Option B+ would affect this reality, we do not expect that this analytical choice affected the results.

An additional simplification in our model was the assumption that persons who discontinue ART progress through disease stages at the same rate as ART-naïve persons. As rapid increases in viral load and decreases in CD4 counts can follow ART interruption,[195] this assumption may have particularly underestimated the proportion of women in later HIV stages in the Option B scenarios, as more women discontinue ART under Option B than Option B+. The net effect of this potential bias on the comparison of Option B vs. Option B+ incidence reductions is difficult to predict, however. On the one hand, greater underestimation of women in later disease stages under Option B (compared to Option B+) could result in greater underestimation of HIV incidence in the Option B scenario than in the Option B+ scenario, as women in later HIV stages are assumed to have higher biological infectiousness. Incidence reductions attributable to Option B+ would thus be over-estimated. On the other hand, faster progression results in higher mortality (and thus a shorter duration of infectiousness), so greater underestimation of progression rates under Option B than under Option B+ could result in overestimation of HIV incidence in the Option B scenario, resulting in underestimation of the relative incidence reduction attributable to Option B+.

Despite these limitations, our findings add to existing evidence that Option B+ can substantially reduce adult HIV incidence in sub-Saharan Africa, even in an era when ART-for-health begins at CD4 counts as high as 499 cells/mm^3. These gains may be particularly great if the removal of CD4 testing barriers by Option B+ results in improved ART uptake for PMTCT. Option B+ is now being implemented in most countries in sub-Saharan Africa where HIV is endemic and fertility is high, suggesting that HIV incidence declines in this region may be even greater than has been projected on the basis of ART-for-health expansion alone. As the optimal realization of these benefits will depend on ART adherence and retention, and because long-term trends in ART adherence and retention under Option B+ remain to be seen, countries implementing Option B+ should make deliberate efforts to encourage and monitor ART adherence and retention, both during pregnancy and after breastfeeding cessation.

Tables and Figures

Table 5.1 Input parameter descriptions and values

Parameter	Description	Value or distribution*	Source
n	Initial size of the entire female population aged 15- 49 years in Lilongwe	271541	130
η	Rate at which young non-pregnant susceptible women enter the sexually active age per year	0.029	Calculated
$\Lambda(t)$	HIV incidence rate at year *t*	Supplement Table A2.1	156
Relative HIV incidence rate by age and pregnant/breastfeeding status			
δ_1	Relative HIV incidence rate comparing women in age cohort 15 – 19 to women in age cohort 25 - 34	0.52	157
δ_2	Relative HIV incidence rate comparing women in age cohort 20 – 24 to women in age cohort 25 – 34	1.02	

* For parameter values that varied across runs, distributions are given as uniform (lower limit, upper limit) or normal (mean, SD)

Table 5.1 Input parameter descriptions and values (continued)

Parameter	Description	Value or distribution*	Source
δ_4	Relative HIV incidence rate comparing women in age cohort 35 – 49 to women in age cohort 25 - 34	0.59	157
$\ln(\varpi)$	Natural log of relative HIV incidence rate comparing either pregnant or breastfeeding women to neither pregnant nor breastfeeding women	Normal (0.77, 0.23)	158
Distribution of HIV stages immediately after primary infection			
π_1	Proportion of newly infected women going directly to asymptomatic stage 1 (CD4>500)	Normal (0.76, 0.013)	159
π_2	Proportion of newly infected women going directly to asymptomatic stage 2 (CD4 350-500)	Normal (0.19, 0.013)	

* For parameter values that varied across runs, distributions are given as uniform (lower limit, upper limit) or normal (mean, SD)

Table 5.1 Input parameter descriptions and values (continued)

Parameter	Description	Value or distribution*	Source
π_3	Proportion of newly infected women going directly to asymptomatic stage 3 (CD4 200-350)	Normal (0.05, 0.008)	159
π_4	Proportion of newly infected women going directly to AIDS stage (CD4 < 200)	Normal (0.00, 0.003)	
Duration of untreated HIV infection stages; effect of ART			
$1/\gamma_1$	Duration of HIV infection in asymptomatic stage 1 (years)	Normal (3.32, 0.13)	159
$1/\gamma_2$	Duration of HIV infection in asymptomatic stage 2 (years)	Normal (2.70, 0.12)	
$1/\gamma_3$	Duration of HIV infection in asymptomatic stage 3 (years)	Normal (5.50, 0.47)	
$1/\gamma_4$	Duration of HIV infection in AIDS stage (years)	Normal (5.06, 0.94)	
φ	Relative disease progression rate due to being on ART	Uniform (0.2, 0.5)	169, 170, 177

* For parameter values that varied across runs, distributions are given as uniform (lower limit, upper limit) or normal (mean, SD)

Table 5.1 Input parameter, description and values (continued)

Parameter	Description	Value or distribution*	Source
ART uptake and drop-out rates			
ϕ^h	Annual ART uptake rate for health for eligible not pregnant women	Table 2	–166 - 168
b^h	Annual ART uptake rate for PMTCT for pregnant /breastfeeding women	Table 2	–166 - 168
$\psi^{0,h}$	Annual ART drop-out rate for non-pregnant/breastfeeding	Uniform (0.03, 0.1)	169 - 176
$\psi^{1,h}$	Annual ART drop-out rate for PMTCT	Uniform (0.03, 0.1)	–169 - 176
ν^h	Proportion of HIV infected pregnant / breastfeeding women on ART and in HIV disease stage *h* who are eligible to continue ART after stopping breastfeeding (Option B vs B+)	Supplement Table A2.2	–153, 160 -162

* For parameter values that varied across runs, distributions are given as uniform (lower limit, upper limit) or normal (mean, SD)

Table 5.1 Input parameter, description and values (continued)

Parameter	Description	Value or distribution*	Source
Aging rate from one age group to the next			
ζ_1	Aging rate from 15-19 to 20-24 (per year)	0.2	Calculated as reciprocal of total number of years in age bracket
ζ_2	Aging rate from 20-24 to 25-34 (per year)	0.2	
ζ_3	Aging rate from 25-34 to 35-49 (per year)	0.1	
ζ_4	Aging rate from 35-49 to > 49 (aging out of the sexually active population) (per year)	0.07	
Fertility and ANC Parameters			
f_c	Age- and calendar time-specific fertility rate for susceptible women in age cohort *c* (per year)	Supplement Table A2.3	178
ω	calendar time-specific rate at which women exit the pregnancy and breastfeeding status (per year)	Supplement Table A2.4	131, 163 - 165

* For parameter values that varied across runs, distributions are given as uniform (lower limit, upper limit) or normal (mean, SD)

Table 5.1 Input parameter, description and values (continued)

Parameter	Description	Value or distribution*	Source
x	Age- and calendar time-specific rate at which women attended antenatal care (per year)	Supplement Table A2.5	131, 163 - 165
$\ln(R^n)$	Natural log of relative fertility rate for HIV+ not on ART compared to HIV uninfected	Normal (0.31, 0.12)	179, 180
$\ln(R^x)$	Natural log of relative fertility rate for HIV+ on ART compared to HIV+ not on ART	Normal (0.55, 0.20)	104
Relative HIV infectiousness			
ρ^1	CD4: 350-499 vs CD4 ≥ 500	0.93	183
ρ^2	CD4: 200 – 349 vs CD4 ≥ 500	1.53	
ρ^3	CD4 < 200 vs CD4 ≥ 500	4.83	
κ	Relative HIV infectiousness comparing individuals on ART to individuals not on ART	0.08	114, 183, 185
α	Relative HIV infectiousness comparing pregnant women to not pregnant women	2.47	185

* For parameter values that varied across runs, distributions are given as uniform (lower limit, upper limit) or normal (mean, SD)

Table 5.2 ART uptake rates for health and PMTCT among eligible women

ART program	CD4 category	Year					
		2000 - 2005‡	2006 - 2010‡	2011§	2012§	2013§	2014¥
ART for Health	≥500	0	0	0	0	0	0
	350 - 499	0	0	0	0	0	Uniform (0.49, 0.61)
	200 - 349†	Uniform (0.05, 0.10)	Uniform (0.10, 0.25)	Uniform(0.49, 0.61)			
	< 200†	Uniform (0.05, 0.10)	Uniform (0.10, 0.25)	Uniform(0.49, 0.61)			
PMTCT*	≥500	0	0	Uniform (0.45, 0.50)	Uniform (0.65, 0.70)	Uniform (0.60, 0.65)	Uniform (0.65, 0.70)
	350 - 499	0	0				
	200 - 349†	Uniform (0.05, 0.10)	Uniform (0.10, 0.25)				
	< 200†	Uniform (0.05, 0.10)	Uniform (0.10, 0.25)				

Sources: 1. Ministry of Health. *Quarterly Report Antiretroviral Treatment Programme in Malawi.* Lilongwe, Malawi: 2004 – 2009

2. Ministry of Health. *Intergrated HIV Program Quarterly Reports* Lilongwe, Malawi: 2010 - 2014.

3. Rosen S, Fox MP. Retention in HIV care between testing and treatment in sub-Saharan Africa: a systematic review. *PLoS medicine.* 2011;8(7):e1001056.

* Values shown for 2011-2015 were applied in Scenarios 1 and 2. The value for 2011 was held constant from 2011 onward in Scenario 3.

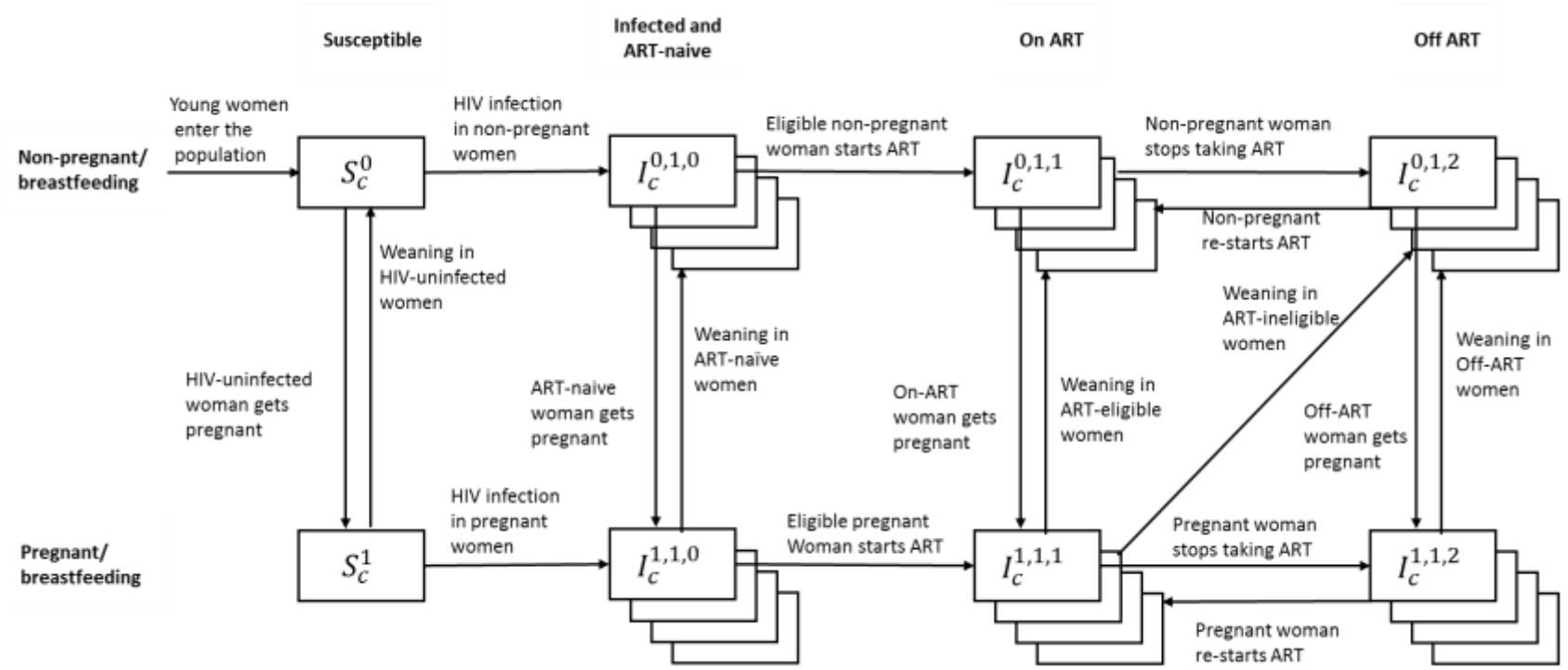
† The uptake (years 2000 – 2010) were applied to the estimated proportion of women in the 200-349 stratum who had CD4 < 250 when the threshold was CD4 < 250

‡ 2000 - 2010 corresponds to CD4 < 250 ART eligibility criteria

§ 2011 - 2013 corresponds to CD4 < 350 ART eligibility criteria

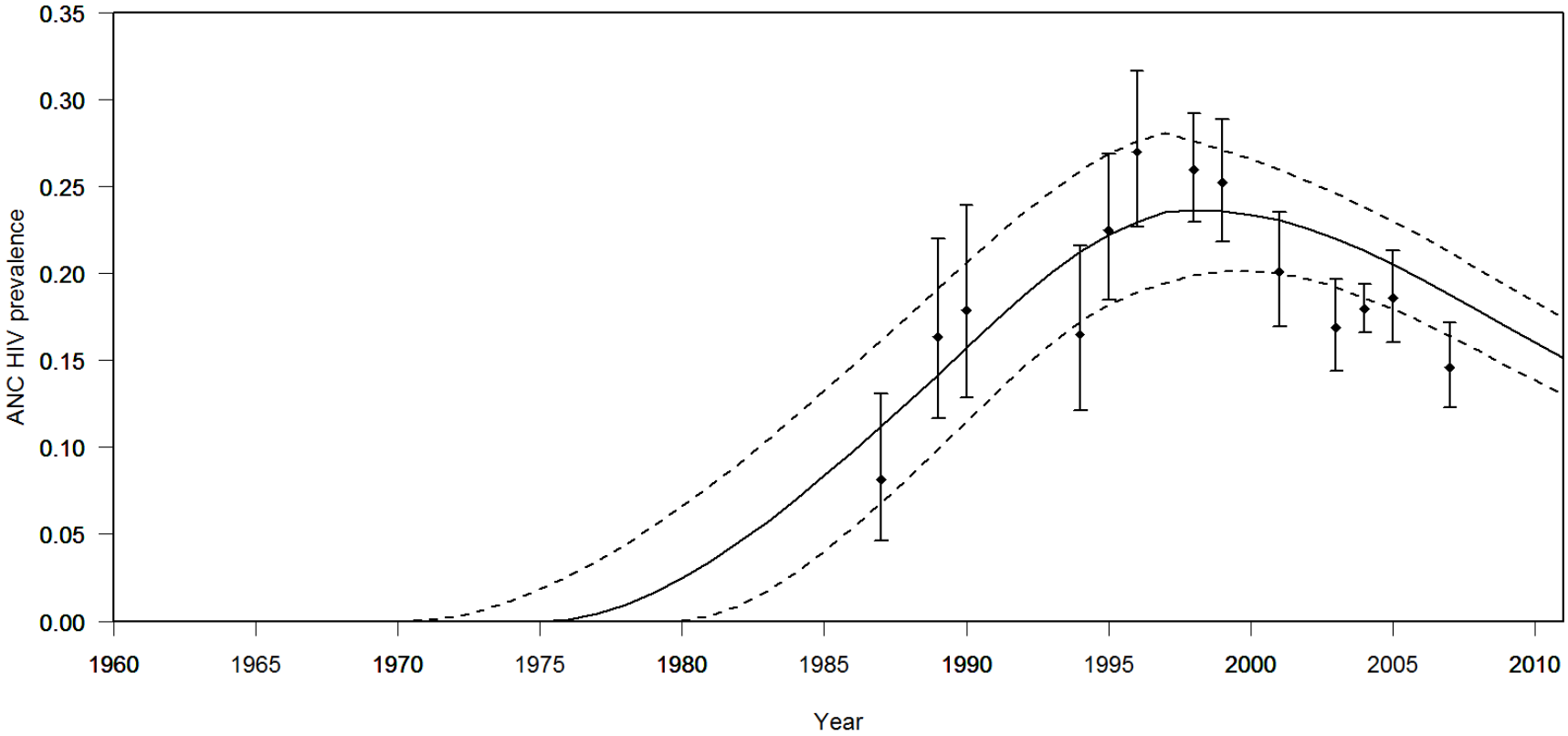
¥ 2014 corresponds to CD4 < 500 ART eligibility criteria

Figure 5.1 Simplified model diagram



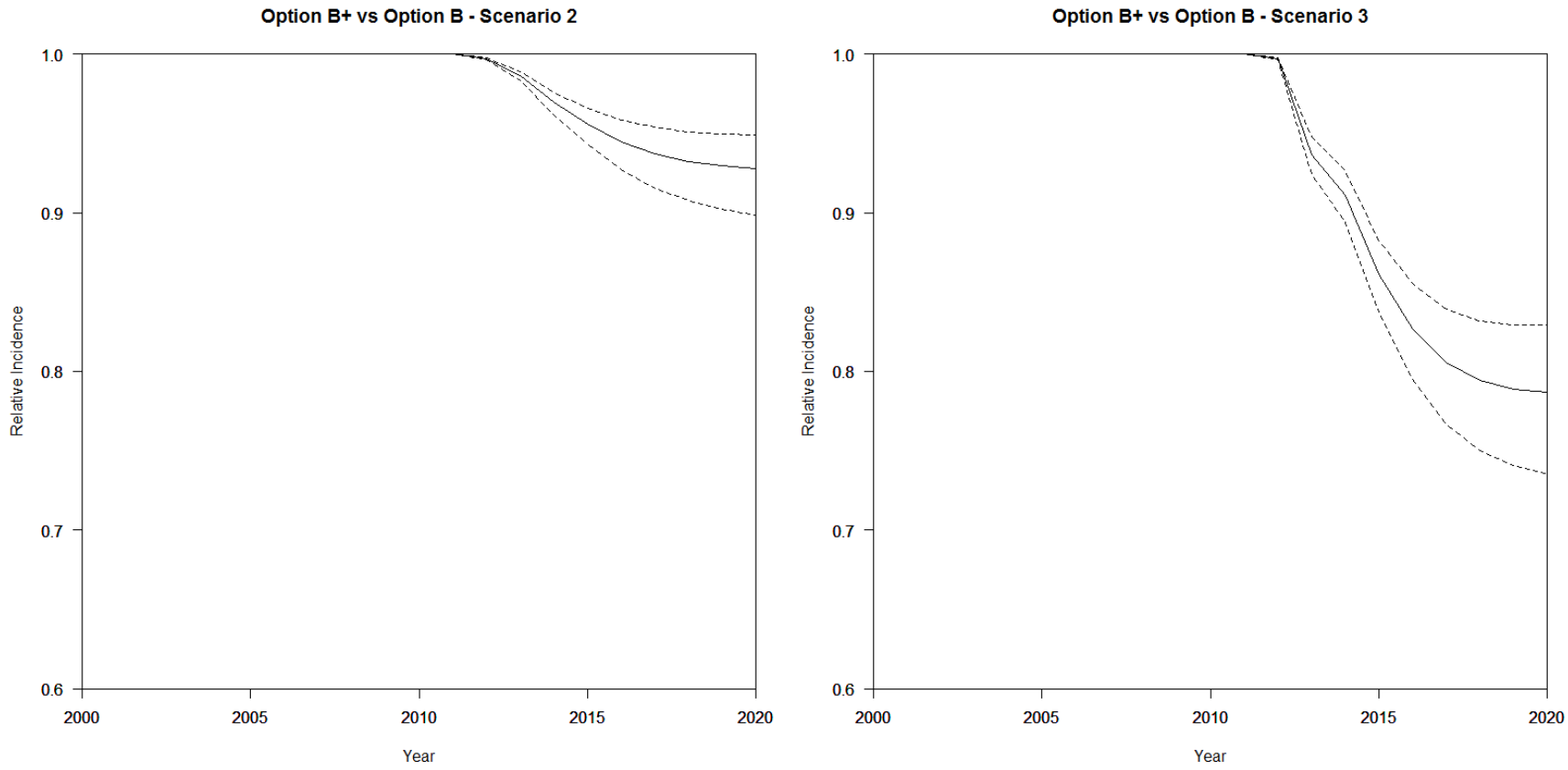
The population of women in the model is stratified by HIV status as HIV-uninfected S_c^p , and HIV-infected $I_c^{p,h,a}$, where the subscript c indicates age cohort (1=15-19, 2=20-24, 3=25-34, and 4=35-49), the subscript *p* indicates pregnancy / breastfeeding status (0 = not pregnant / breastfeeding, 1 = pregnant / breastfeeding), the subscript *h* represents HIV stage among HIV-infected women (1 = CD4 ≥500, 2 = 350 ≤ CD4 ≤499, 3 = 200 ≤ CD4 ≤349, and 4 = CD4 < 200), and the subscript *a* represents ART status among HIV-infected women (0 = ART naïve, 1 = on ART, 2 = off ART). The "stacked" boxes represent disease stages. Not shown in the diagram is the process of aging from one age group to the next.

Figure 5.2 Antenatal HIV prevalence in Lilongwe, Malawi



HIV prevalence data from Lilongwe antenatal clinic are shown as points with corresponding 95% confidence intervals. The solid line is the median HIV prevalence and the dashed lines are the 2.5th and 97.5th percentile at each time point generated from the model output.

Figure 5.3 Relative HIV incidence in men comparing Option B+ to Option B strategies



The solid line is the median relative HIV incidence in men and the dashed lines are the 2.5th and 97.5th percentile at each time point generated from the model output.

Option B+ vs Option B – Scenario 2 compares Option B+ to Option B, with ART uptake values in the period 2011-2020 assumed to be the same for Option B (scenario 2) as those assumed for Option B+ (scenario 1)

Option B+ vs Option B – Scenario 3 compares Option B+ to Option B, with ART uptake values in the period 2011-2020 assumed to remain at 2011 levels for the Option B scenario (scenario 3)

CHAPTER SIX: DISCUSSION

Option B+ is a simplified approach to PMTCT[5] that has now been recommended by WHO for all countries with a generalized HIV epidemic.[8] Under Option B+, all confirmed HIV-infected pregnant or breastfeeding women are started on life-long ART regardless of WHO Clinical Stage or CD4 cell count. Besides preventing MTCT, the Option B+ approach has other potential ancillary public health benefits beyond those offered by Option A and Option B, including improved infant and maternal health, greater uptake of ART due to removal of CD4-related obstacles, and continued prevention of sexual HIV transmission from HIV-infected women beyond pregnancy and breastfeeding.[5,102]

In this work, we sought to advance understanding of ART effects in the Option B+ era. More specifically, we assessed the relationship between ART exposure during pregnancy and preterm birth, and we quantified the impact of Option B+ on the adult HIV / AIDS burden through reduced heterosexual transmission. The results and implications of each analysis are summarized below.

Aim 1: Time of ART initiation and preterm birth

Summary of Results

In Aim 1, we estimated the risk of preterm birth among singleton live infants born to HIV-infected women delivering at ≥ 27 weeks of gestation at Bwaila Hospital in Lilongwe, Malawi between April 1, 2012 and November 15, 2015. We compared the risk of preterm birth

according to ART exposure during pregnancy and (for those on ART at delivery) time of ART initiation during pregnancy. We hypothesized that a) women who are on ART during pregnancy have a lower risk of delivering preterm infants than those not on ART, and b) women who initiate ART earlier in pregnancy have a lower risk of delivering preterm infants compared to women who initiate ART later or never initiated ART during pregnancy.

Among 3074 women who had singleton live births at 27+ weeks of gestation and initiated ART before 27 weeks of gestation or never initiated ART during pregnancy, most women had initiated ART before pregnancy (N=1139, 37.0%) or during the second trimester (N=1503, 48.9%). A total of 731 preterm births were observed during the study period (risk = 24%; 95% CI: 22% - 25%).

In the analysis of all preterm births vs full term births, there was not a clear trend in the relationship between timing of ART initiation and risk of preterm birth; the aRRs for preterm birth were 0.78 (95% CI: 0.57 – 1.08), 1.03 (95% CI: 0.72 – 1.49), and 0.92 (95% CI: 0.67 – 1.25) for initiating ART before pregnancy, during the 1st trimester, and during the 2nd trimester, respectively, after adjustment for mother's age and parity. ART initiation at any point before delivery appeared strongly protective against extremely to very preterm birth (aRR = 0.43; 95% CI: 0.26 – 0.72). Our results also suggested that ART was protective against extremely to very preterm birth at all three initiation times assessed separately: before pregnancy (aRR = 0.42; 95% CI: 0.24 – 0.73), in the 1st trimester (aRR = 0.54; 95%CI: 0.27 – 1.10), and in the 2nd trimester (aRR = 0.42; 95% CI: 0.24 – 0.72).

Interpretation

Our findings highlight the importance of HIV-infected women being on ART during pregnancy for the benefit to the developing fetus as well as their own health. ART during pregnancy did not appear to increase the risk of preterm birth in our study, and initiation prior to

conception appeared protective. Importantly, ART initiation prior to conception appeared strongly protective against extremely to very preterm birth (27 - < 32 weeks of gestation).

Public health significance

Option B+ is now being implemented in most countries in sub-Saharan Africa with a generalized HIV epidemic[8] and high proportion of preterm births.[23] As the Option B+ program matures, we expect the proportion of women on lifelong ART following a prior pregnancy to grow. Consequently, we expect the proportion of women on ART prior to conception to increase. Our finding that the risk of preterm birth was much lower in this group gives us hope that incidence of preterm birth among HIV-infected mothers will decrease as the time since Option B+ implementation increases.

Neonatal and infant mortality is high among preterm births, with only 30% of babies born between 28 and 32 weeks in low-income countries surviving.[27] Our finding that being on ART during pregnancy is protective against extremely to very preterm birth, regardless of time of ART initiation, is especially encouraging. Increased ART uptake in the Option B+ era could therefore have a profound impact on neonatal mortality in developing countries where advanced nursery facilities for very preterm babies are not readily available.

Limitations

Gestational age assessment in this study was based on last menstrual period, which is not as accurate as ultrasound in dating pregnancy. Our determination of preterm status and ART initiation status based on gestational age may have resulted in misclassified preterm status and ART initiation time within pregnancy. We also note that our study population was confined to those who initiated ART before 27 weeks and gave birth at 27+ weeks, so we were not able to assess the effects of third-trimester ART initiation or the risk of extremely preterm birth prior to 27 weeks.

Our analysis is based on routinely collected data which is often characterized by limited inclusion of relevant variables, missing data, and/or erroneous data. We did not have information on several variables that may have resulted in unmeasured (and unaddressed) confounding. In particular, we did not have information on ART adherence and antenatal care attendance prior to delivery. As we did not have information on ART adherence or continuity, ART-exposed women were assigned to exposure categories according to timing of ART initiation regardless of whether they were truly on therapy during the entire period or not. However, ART adherence during pregnancy is generally very high, so we would not expect any unmeasured variability in adherence to have substantially affected our results.

HIV-infected women not previously on ART are initiated on life-long ART during an ANC visit,[154] in addition to standard prenatal care. In the likely event that the women who had never initiated ART prior to delivery were less likely to have had access to prenatal care, then the higher risk of preterm births among those who did not initiate ART may not be fully attributable to lack of ART during pregnancy.

Future Research Directions

Now that Option B+ is being implemented in many developing countries, there will be a continued need and new opportunities for improving our understanding of the effect of ART duration on birth outcomes. In this study, we only estimated the risk of preterm birth, using routinely collected clinical data. Well-designed prospective cohort studies that follow HIV-infected pregnant women from antenatal care up to delivery and collect data on important covariates would provide opportunities to estimate the causal effect of ART on preterm birth. Such studies could also assess the effects of ART on other birth outcomes such as stillbirth, low birthweight and congenital development issues.

As described above and in earlier chapters, ART duration during pregnancy is intrinsically linked to length of gestation, making it challenging to estimate the effect of ART

across the full pregnancy spectrum. To circumvent this complexity, we restricted our analysis to women who initiated ART before 27 weeks of gestation or never initiated ART and delivered at ≥ 27 weeks of gestation. Future studies with innovative causal inference methodologies may allow assessment of ART initiation timing and its effects on preterm birth without the restrictions we imposed.

Aim 2: Option B+ and female-to-male HIV transmission

Summary of Results

In this aim, we developed a mathematical model to estimate the expected relative reduction in HIV incidence among men in Lilongwe, Malawi under Option B+ versus Option B. Our hypothesis was that ART initiation among HIV-infected pregnant women under Option B+ would provide greater reductions in female-to-male transmission than under Option B.

Comparing Option B+ to Option B with the assumption that ART uptake values in the period 2011-2020 were the same for both strategies, the estimated relative incidence (RI) under Option B+ was 4% lower (median RI = 0.96; 95% CI: 0.94 – 0.97) in 2015 and was projected to be 7% lower (median RI = 0.93; 95% CI: 0.90 – 0.95) by 2020. Comparing Option B+ to the Option B scenario in which ART uptake values in the period 2011-2020 were assumed to remain at 2011 levels (i.e., not to increase as they did under Option B+), the estimated RI under Option B+ was 14% lower (median RI = 0.86; 95% CI: 0.84 – 0.88) in 2015 and was projected to be 21% lower (median RI = 0.79; 95% CI: 0.74 – 0.83) by 2020.

Interpretation

Heterosexual HIV transmission is the main mode of HIV transmission in the sub-Saharan Africa region. In addition to preventing MTCT, our results suggest that the Option B+ strategy has considerable potential to reduce female-to-male HIV transmission over its first nine years, particularly if it greatly increases ART uptake.

Public health significance

More reproductive-aged women are expected to be on ART due to initiation during pregnancy as Option B+ matures in sub-Saharan Africa. Our findings suggest that as more women are started on ART during pregnancy and continue for life, female-to-male HIV transmission will decrease. As this ancillary benefit of reducing transmission will be maximized with high ART adherence, countries implementing Option B+ should strive to encourage adherence to ART during pregnancy and after breastfeeding cessation. If high adherence can be maintained, then the expansion of Option B+ in this region could result in greater HIV incidence reductions than have been predicted on the basis of expanded ART-for-health alone.

Limitations

Mathematical modeling involves simplifying assumptions in order to develop tractable models. As a simplification, we only focused on female-to-male transmission, thus ignoring the resultant reduction in male-to-female transmission due to reduced HIV prevalence among males. As such, the reduction in overall heterosexual incidence attributable to Option B+ will likely be larger than estimated for female-to-male transmission only. We also assumed that persons who discontinue ART progress through disease stages at the same rate as ART-naïve persons, although rapid increases in viral load and decreases in CD4 counts can follow ART interruption. As described in Chapter 6, this assumption may have disproportionately underestimated the proportion of women in later HIV stages in the Option B scenarios (versus

the Option B+ scenario), but the effect of this underestimation on male-to-female transmission reductions is difficult to predict in our highly complex model.

Future Research Directions

Heterosexual HIV transmission is a complex process that is affected by many factors, including sexual mixing patterns, sexual contact rates, and the probability of transmission per sexual contact. Our model and another previous model [192] did not model heterosexual transmission as an explicit function of these phenomena. In both of these models only the relative HIV incidence reduction in men was evaluated without taking into account the subsequent reductions that would occur among women as a result of reduced HIV prevalence in men. Future transmission modeling work comparing Option B+ to Option B could incorporate male model compartments and explicitly model male-female interactions, allowing estimation of absolute reductions in HIV incidence and inclusion of non-linear dynamics. Perhaps more importantly, updated models may be necessary as treatment guidelines continue to evolve. Additional models developed for other settings that implement Option B+ could also expand our understanding of PMTCT programs' ancillary benefits for heterosexual transmission.

Conclusions

HIV is pandemic in sub-Saharan Africa, with particularly high incidence and prevalence among reproductive-aged women. Encouraging reductions in mother-to-child transmission have occurred because of the effectiveness of ART in preventing vertical transmission. Here we have shown that PMTCT programs – in particular, the Option B+ strategy – have additional public health benefits apart from preventing mother-to-child transmission.

Our results indicated that PMTCT Option B+ may reduce the risk of extremely to very preterm birth among HIV-infected women by increasing the likelihood that they will be on ART during pregnancy, and that it may reduce the risk of preterm birth overall by increasing the

likelihood that HIV-infected women will be on ART prior to subsequent conceptions. We also found that compared to the Option B strategy, the Option B+ strategy is likely to prevent more cases of female-to-male transmission, conferring additional benefits beyond the PMTCT for which it is primarily intended. Furthermore, Option B+ enables an additional pathway for ART uptake in sub-Saharan Africa, allowing greater reductions in population-level HIV incidence than would be expected from “ART-for-health” alone. As such, Option B+ appears to be very positive addition to the HIV treatment and prevention arsenal in the current era of the HIV epidemic.

APPENDIX 1: AIM 2 MODEL EQUATIONS

Model structure and equations

Model compartments and parameter description

Our model was implemented using differential equations capturing the dynamics of women in the population compartments as follows:

S_c^p represent susceptible women in age cohort c (1, 2, 3 , 4) and pregnant/breastfeeding status p (0, 1).

$I_c^{p,h,a}$ represent HIV infected women in age cohort c, pregnant/breastfeeding status p (0, 1), HIV disease stage h (1, 2, 3, 4), and ART status a (0,1, 2).

Below are the definitions of the parameters in the model:

$\eta(t)$ is rate at which young non-pregnant susceptible women enter the sexually active age at time t

$\lambda_c(t)$ is the age- (c) and calendar time-specific HIV incidence rate for not pregnant / breastfeeding women at time t

ϖ is the relative HIV incidence rate comparing pregnant/breastfeeding women to not pregnant women

δ_c is the relative HIV incidence rate comparing women in age c to women in age cohort 3

π_h is the proportion of newly HIV-infected women progressing directly to HIV disease stage h

$\phi^h(t)$ is the calendar time-specific ART initiation rate among neither pregnant nor breastfeeding women eligible for ART for health in HIV disease stage h .

$x(t)$ is age- and calendar time-specific antenatal uptake rate

$b^h(t)$ is the calendar time-specific ART uptake rate for PMTCT among either pregnant or breastfeeding women under the PMTCT program being considered at time t. (option A, Option B, or Option B+)

$\psi^{0,h}$ is the annual ART dropout rate among neither pregnant nor breastfeeding women in HIV disease stage *h*

$\psi^{1,h}$ is the annual ART dropout rate among either pregnant or breastfeeding women in HIV disease stage *h*.

$\omega(t)$ is the calendar time-specific rate at which women exit the pregnancy and breastfeeding status $\left(\omega = {}^{1}/_{pregnancy\ duration + breastfeeding\ duration}\right)$

$\nu^h(t)$ is the calendar time and HIV disease stage -specific proportion of HIV infected pregnant / breastfeeding women on ART eligible to continue ART after stopping breastfeeding

$f_c(t)$ is the age- and calendar time-specific fertility rate for HIV-uninfected women in age cohort *c*

R^n is the relative fertility rate comparing untreated HIV infected women in age category c to HIV uninfected women in age cohort *c*

R^x is the relative fertility rate comparing HIV infected women on ART to untreated HIV-infected women

γ_h is the HIV disease progression rate for individuals in disease stage *h.*

φ is the effect of ART on HIV disease progression

ζ_c is the rate at which women age from cohort c to age cohort *c+1* ($\zeta_c = {}^{1}/_{interval\ c}$)

ρ^h Relative HIV infectiousness due to disease stage comparing stages 2, 3, 4 to stage 1

κ Relative HIV infectiousness comparing individuals on ART to individuals not on ART

α Relative HIV infectiousness comparing pregnant women to not pregnant women

Description of the model equations

Using the parameters described above, we used differential equations to describe the rates of change in the women population compartments as follows:

a. Not currently pregnant/breastfeeding HIV uninfected women

i. $\frac{dS_1^0}{dt} = \eta + \omega S_1^1 - (\pi_1 + \pi_2 + \pi_3 + \pi_4)\lambda_1^r S_1^0 - f_1 S_1^0 - \zeta_1 S_1^0$ for *r* = 1, 2, 3

ii. $\frac{dS_c^0}{dt} = \omega S_c^1 + \zeta_{c-1} S_{c-1}^0 - (\pi_1 + \pi_2 + \pi_3 + \pi_4)\lambda_c^r S_c^0 - f_c S_c^0 - \zeta_c S_c^0$ for c = 2, 3, 4; *r* = 1, 2, 3

b. Currently pregnant/breastfeeding HIV uninfected women

i. $\frac{dS_1^1}{dt} = f_1 S_1^0 - (\pi_1 + \pi_2 + \pi_3 + \pi_4)\varpi\lambda_1^r S_1^1 - \omega S_1^1 - \zeta_1 S_1^1$ for *r* = 1, 2 , 3

ii. $\frac{dS_c^1}{dt} = f_c S_c^0 + \zeta_{c-1} S_{c-1}^1 - (\pi_1 + \pi_2 + \pi_3 + \pi_4)\varpi\lambda_c^r S_c^1 - \omega S_c^1 - \zeta_c S_c^1$ for c = 2, 3, 4; *r* = 1, 2, 3

c. Not currently pregnant/breastfeeding HIV infected women

<u>ART naïve</u>

i. $\frac{dI_1^{0,1,0}}{dt} = \pi_1 \lambda_1^r S_1^0 + \omega I_1^{1,1,0} - \gamma_1 I_1^{0,1,0} - R^n f_1 I_1^{0,1,0} - \phi^1 I_c^{0,1,0} - \zeta_1 I_1^{0,1,0}$ for *r* = 1, 2, 3

ii. $\frac{dI_c^{0,1,0}}{dt} = \pi_1 \lambda_c^r S_c^0 + \zeta_{c-1} I_{c-1}^{0,1,0} + \omega I_c^{1,1,0} - \gamma_1 I_c^{0,1,0} - R^n f_c I_c^{0,1,0} - \phi^1 I_c^{0,1,0} - \zeta_c I_c^{0,1,0}$ for *c* = 2, 3, 4; *r* = 1, 2, 3

iii. $\frac{dI_1^{0,h,0}}{dt} = \pi_h \lambda_1^r S_1^0 + \gamma_{h-1} I_1^{0,h-1,0} + \omega I_1^{1,h,0} - \gamma_h I_1^{0,h,0} - R^n f_1 I_1^{0,h,0} - \phi^h I_1^{0,h,0} - \zeta_1 I_1^{0,h,0}$ for *h* = 2, 3, 4; *r* = 1, 2, 3

iv. $\frac{dI_c^{0,h,0}}{dt} = \pi_h \lambda_c^r S_c^0 + \gamma_{h-1} I_c^{0,h-1,0} + \zeta_{c-1} I_{c-1}^{0,h,0} + \omega I_c^{1,h,0} - \gamma_h I_c^{0,h,0} - R^n f_c I_c^{0,h,0} - \phi^h I_c^{0,h,0} - \zeta_c I_c^{0,h,0}$ for *c* = 2, 3, 4; *h* = 2,3, 4; *r* = 1, 2, 3

On ART

i. $\frac{dI_1^{0,1,1}}{dt} = \phi^1 I_1^{0,1,0} + \nu\omega I_1^{1,1,1} - \varphi\gamma_1 I_1^{0,1,1} - R^x R^n f_1 I_1^{0,1,1} - \psi^{0,1} I_1^{0,1,1} - \zeta_1 I_1^{0,1,1}$

ii. $\frac{dI_c^{0,1,1}}{dt} = \phi^1 I_c^{0,1,0} + \zeta_{c-1} I_{c-1}^{0,1,1} + \nu\omega I_c^{1,1,1} - \varphi\gamma_1 I_c^{0,1,1} - R^x R^n f_c I_c^{0,1,1} - \psi^{0,1} I_c^{0,1,1} - \zeta_c I_c^{0,1,1}$

for c = 2, 3, 4

iii. $\frac{dI_1^{0,h,1}}{dt} = \varphi\gamma_{h-1} I_1^{0,h-1,1} + \phi^h I_1^{0,h,0} + \nu\omega I_1^{1,h,1} - \varphi\gamma_h I_1^{0,h,1} - R^x R^n f_1 I_1^{0,h,1} - \psi^{0,h} I_1^{0,h,1} -$

$\zeta_1 I_1^{0,h,1}$ for h= 2, 3

iv. $\frac{dI_c^{0,h,1}}{dt} = \varphi\gamma_{h-1} I_c^{0,h-1,1} + \phi^h I_c^{0,h,0} + \zeta_{c-1} I_{c-1}^{0,h,1} + \nu\omega I_c^{1,h,1} - \varphi\gamma_h I_c^{0,h,1} - R^x R^n f_c I_c^{0,h,1} -$

$\psi^{0,h} I_c^{0,h,1} - \zeta_c I_c^{0,h,1}$ for c = 2,3,4 ; h = 2, 3

v. $\frac{dI_1^{0,4,1}}{dt} = \varphi\gamma_3 I_1^{0,3,1} + \phi^4 I_1^{0,4,0} + \phi^4 I_1^{0,4,2} + \nu\omega I_1^{1,4,1} - R^x R^n f_1 I_1^{0,4,1} - \psi^{0,4} I_1^{0,4,1} - \zeta_1 I_1^{0,4,1} -$

$\varphi\gamma_4 I_1^{0,4,1}$

vi. $\frac{dI_c^{0,4,1}}{dt} = \varphi\gamma_3 I_c^{0,3,1} + \phi^4 I_c^{0,4,0} + \phi^{.4} I_c^{0,4,2} + \zeta_{c-1} I_{c-1}^{0,4,1} + \nu\omega I_c^{1,4,1} - R^x R^n f_c I_c^{0,4,1} - \psi^{0,4} I_c^{0,4,1} -$

$\zeta_c I_c^{0,4,1} - \varphi\gamma_4 I_c^{0,4,1}$ for c = 2,3,4

ART dropouts

i. $\frac{dI_1^{0,1,2}}{dt} = \psi^{0,1} I_1^{0,1,1} + \omega I_1^{1,1,2} + (1-\nu)\omega I_1^{1,1,1} - \gamma_1 I_1^{0,1,2} - R^n f_1 I_1^{0,1,2} - \zeta_1 I_1^{0,1,2}$

ii. $\frac{dI_c^{0,1,2}}{dt} = \psi^{0,1} I_c^{0,1,1} + \zeta_{c-1} I_{c-1}^{0,1,2} + \omega I_c^{1,1,2} + (1-\nu)\omega I_c^{1,1,1} - \gamma_1 I_c^{0,1,2} - R^n f_c I_c^{0,1,2} - \zeta_c I_c^{0,1,2}$

for c = 2, 3, 4

iii. $\frac{dI_1^{0,h,2}}{dt} = \gamma_{h-1} I_1^{0,h-1,2} + \psi^{0,h} I_1^{0,h,1} + \omega I_1^{1,h,2} + (1-\nu)\omega I_1^{1,h,1} - \gamma_h I_1^{0,h,2} - R^n f_1 I_1^{0,h,2} - \zeta_1 I_1^{0,h,2}$

for h = 2, 3

iv. $\frac{dI_c^{0,h,2}}{dt} = \gamma_{h-1} I_c^{0,h-1,2} + \psi^{0,h} I_c^{0,h,1} + \zeta_{c-1} I_{c-1}^{0,h,2} + \omega I_c^{1,h,2} + (1-\nu)\omega I_c^{1,h,1} - \gamma_h I_c^{0,h,2} -$

$R^n f_c I_c^{0,h,2} - \zeta_c I_c^{0,h,2}$ for c = 2, 3, 4; h = 2, 3

v. $\frac{dI_1^{0,4,2}}{dt} = \gamma_3 I_1^{0,3,2} + \psi^{0,4} I_1^{0,4,1} + \omega I_1^{1,4,2} + (1-\nu)\omega I_1^{1,4,1} - R^n f_1 I_1^{0,4,2} - \phi^{0.4} I_1^{0,4,2} - \zeta_1 I_1^{0,4,2} - \gamma_4 I_1^{0,4,2}$

vi. $\frac{dI_c^{0,4,2}}{dt} = \gamma_3 I_c^{0,3,2} + \psi^{0,4} I_c^{0,4,1} + \zeta_{c-1} I_{c-1}^{0,4,2} + \omega I_c^{1,4,2} + (1-\nu)\omega I_c^{1,4,1} - R^n f_c I_c^{0,4,2} - \phi^{0,4} I_c^{0,4,2} - \zeta_c I_c^{0,4,2} - \gamma_4 I_c^{0,4,2}$ for *c* = 2, 3, 4

d. Currently pregnant/breastfeeding HIV infected women

ART naïve

i. $\frac{dI_1^{1,1,0}}{dt} = \pi_1 \varpi \lambda_1^r S_1^1 + R^n f_1 I_1^{0,1,0} - \gamma_1 I_1^{1,1,0} - \omega I_1^{1,1,0} - xb^1 I_1^{1,1,0} - \zeta_1 I_1^{1,1,0}$

for *r* = 1, 2, 3

ii. $\frac{dI_c^{1,1,0}}{dt} = \pi_1 \varpi \lambda_c^r S_c^1 + \zeta_{c-1} I_{c-1}^{1,1,0} + R^n f_c I_c^{0,1,0} - \gamma_1 I_c^{1,1,0} - \omega I_c^{1,1,0} - xb^1 I_c^{1,1,0} - \zeta_c I_c^{1,1,0}$ for *c* = 2, 3, 4; *r* = 1, 2, 3

iii. $\frac{dI_1^{1,h,0}}{dt} = \pi_h \varpi \lambda_1^r S_1^1 + \gamma_{h-1} I_1^{1,h-1,0} + R^n f_1 I_1^{0,h,0} - \gamma_h I_1^{1,h,0} - \omega I_1^{1,h,0} - xb^h I_1^{1,h,0} - \zeta_1 I_1^{1,h,0}$

for *h* = 2, 3, 4; *r* = 1, 2, 3

iv. $\frac{dI_c^{1,h,0}}{dt} = \pi_h \varpi \lambda_c^r S_c^1 + \gamma_{h-1} I_c^{1,h-1,0} + \zeta_{c-1} I_{c-1}^{1,h,0} + R^n f_c I_c^{0,h,0} - \gamma_h I_c^{1,h,0} - \omega I_c^{1,h,0} - xb^h I_c^{1,h,0} - \zeta_c I_c^{1,h,0}$ for *c* = 2, 3, 4; *h* = 2, 3, 4; *r* = 1, 2, 3

On ART

i. $\frac{dI_1^{1,1,1}}{dt} = xb^1 I_1^{1,1,0} + xb^1 I_1^{1,1,2} + R^x R^n f_1 I_1^{0,1,1} - \varphi\gamma_1 I_1^{1,1,1} - \nu\omega I_1^{1,1,1} - (1-\nu)\omega I_1^{1,1,1} - \psi^{1,1} I_1^{1,1,1} - \zeta_1 I_1^{1,1,1}$

ii. $\frac{dI_c^{1,1,1}}{dt} = xb^1 I_c^{1,1,0} + xb^1 I_c^{1,1,2} + \zeta_{c-1} I_{c-1}^{1,1,1} + R^x R^n f_c I_c^{0,1,1} - \varphi\gamma_1 I_c^{1,1,1} - \nu\omega I_c^{1,1,1} - (1-\nu)\omega I_c^{1,1,1} - \psi^{1,1} I_c^{1,1,1} - \zeta_c I_c^{1,1,1}$ for *c* = 2, 3, 4

iii. $\frac{dI_1^{1,h,1}}{dt} = \varphi\gamma_{h-1}I_1^{1,h-1,1} + xb^hI_1^{1,h,0} + xb^hI_1^{1,h,2} + R^xR^nf_1I_1^{0,h,1} - \varphi\gamma_hI_1^{1,h,1} - \nu\omega I_1^{1,h,1} - (1 - \nu)\omega I_1^{1,h,1} - \psi^{1,h}I_1^{1,h,1} - \zeta_1I_1^{1,h,1}$ for *c = 1 and h* = 2, 3, 4

iv. $\frac{dI_c^{1,h,1}}{dt} = \varphi\gamma_{h-1}I_c^{1,h-1,1} + xb^hI_c^{1,h,0} + xb^hI_c^{1,h,2} + \zeta_{c-1}I_{c-1}^{1,h,1} + R^xR^nf_cI_c^{0,h,1} - \varphi\gamma_hI_c^{1,h,1} - \nu\omega I_c^{1,h,1} - (1 - \nu)\omega I_c^{1,h,1} - \psi^{1,h}I_c^{1,h,1} - \zeta_cI_c^{1,h,1}$ for *c* = 2, 3, 4; *h* = 2, 3, 4

ART dropouts

i. $\frac{dI_1^{1,1,2}}{dt} = \psi^{1,1}I_1^{1,1,1} + R^nf_1I_1^{0,1,2} - \gamma_1I_1^{1,1,2} - \omega I_1^{1,1,2} - xb^1I_1^{1,1,2} - \zeta_1I_1^{1,1,2}$

ii. $\frac{dI_c^{1,1,2}}{dt} = \psi^{1,1}I_c^{1,1,1} + \zeta_{c-1}I_{c-1}^{1,1,2} + R^nf_cI_c^{0,1,2} - \gamma_1I_c^{1,1,2} - \omega I_c^{1,1,2} - xb^1I_c^{1,1,2} - \zeta_cI_c^{1,1,2}$

for *c = 2,3,4*

iii. $\frac{dI_1^{1,h,2}}{dt} = \gamma_{h-1}I_1^{1,h-1,2} + \psi^{1,h}I_1^{1,h,1} + R^nf_1I_1^{0,h,2} - \gamma_hI_1^{1,h,2} - \omega I_1^{1,h,2} - xb^hI_1^{1,h,2} - \zeta_1I_1^{1,h,2}$

for *c=1 and h*= 2, 3, 4

iv. $\frac{dI_c^{1,h,2}}{dt} = \gamma_{h-1}I_c^{1,h-1,2} + \psi^{1,h}I_c^{1,h,1} + \zeta_{c-1}I_{c-1}^{1,h,2} + R^nf_cI_c^{0,h,2} - \gamma_hI_c^{1,h,2} - \omega I_c^{1,h,2} - xb^hI_c^{1,h,2} - \zeta_cI_c^{1,h,2}$ for *c* = 2, 3, 4*; h*= 2, 3, 4

HIV incidence rate among women

Age – and calendar time-specific HIV incidence rates $\lambda_c(t)$ among not pregnant women were derived from the total calendar time-specific HIV incidence rates $\Lambda(t)$ in the population, relative HIV incidence comparing women in age cohort c to age cohort 3 δ_c, and relative HIV incidence comparing pregnant / breastfeeding women to not pregnant women ϖ as follows:

$$\Lambda(t) = \frac{\left(\delta_1(S_1^0 + \varpi S_1^1) + \delta_2(S_2^0 + \varpi S_2^1) + (S_3^0 + \varpi S_3^1) + \delta_4(S_4^0 + \varpi S_4^1)\right)\lambda_3(t)}{\sum_{c=1}^{4}\sum_{p=0}^{1}S_c^p}$$

$$\lambda_3(t) = \frac{\Lambda(t)\sum_{c=1}^{4}\sum_{p=0}^{1}S_c^p}{\delta_1(S_1^0 + \varpi S_1^1) + \delta_2(S_2^0 + \varpi S_2^1) + (S_3^0 + \varpi S_3^1) + \delta_4(S_4^0 + \varpi S_4^1)}$$

Fertility

Age- and calendar time-specific fertility rate for HIV negative f_c , HIV positive but not on ART f_{cx}^0 , and HIV positive on ART f_{cx}^1 were derived from total age- and calendar time-specific fertility rate f_{cT} using fertility rate ratios R^n comparing fertility rates in HIV positive to fertility rates in HIV negative women and fertility rate ratios R^x comparing fertility rates in HIV positive women on ART to HIV positive women not on ART as follows:

$$f_{cT} = \frac{\left(S_c^o + R^n \sum_{h=1}^{4}\left(I_c^{0,h,0} + I_c^{0,h,2}\right) + R^x R^n \sum_{h=1}^{4} I_c^{0,h,1}\right) f_c}{N_c^0}$$

where $N_c^0 = S_c^0 + \sum_{h=1}^{4}\left(I_c^{0,h,0} + I_c^{0,h,1} + I_c^{0,h,2}\right)$, *c* = 1, 2, 3, 4

$$f_c = \frac{f_{cT} N_c^0}{S_c^o + R^n \sum_{h=1}^{4}\left(I_c^{0,h,0} + I_c^{0,h,2}\right) + R^x R^n \sum_{h=1}^{4} I_c^{0,h,1}}$$

HIV transmission from women to men

HIV-infected women will infect their male sexual partners at a constant transmission rate $\beta(t)$ that will be modified by relative infectiousness due to disease stage ρ^h, ART treatment κ, and pregnancy status α with asymptomatic stage 1, not on ART, and not pregnant women as referent.

Total HIV incidence in men (*IM*):

$$IM = \beta(t) \sum_{c=1}^{4} \sum_{h=1}^{4} \rho^h \left\{\left(I_c^{0,h,0} + \alpha I_c^{1,h,0}\right) + \left(I_c^{0,h,2} + \alpha I_c^{1,h,2}\right) + \kappa\left(I_c^{0,h,1} + \alpha I_c^{1,h,1}\right)\right\}$$

APPENDIX 2: AIM 2 SUPPLEMENTAL TABLES

Table A2.1 HIV incidence rates

Year	Incidence rate
1990	Normal(0.0229, 0.0013)
1991	Normal(0.0243, 0.0011)
1992	Normal(0.0248, 0.0011)
1993	Normal(0.0249, 0.0011)
1994	Normal(0.0242, 0.0011)
1995	Normal(0.0233, 0.0009)
1996	Normal(0.0224, 0.0008)
1997	Normal(0.0212, 0.0008)
1998	Normal(0.0200, 0.0007)
1999	Normal(0.0187, 0.0007)
2000	Normal(0.0174, 0.0006)
2001	Normal(0.0161, 0.0006)
2002	Normal(0.0150, 0.0005)
2003	Normal(0.0138, 0.0005)
2004	Normal(0.0128, 0.0004)

Table A2.1 HIV incidence rates (continued)

2005	Normal(0.0117, 0.0004)
2006	Normal(0.0107, 0.0004)
2007	Normal(0.0098, 0.0004)
2008	Normal(0.0089, 0.0005)
2009	Normal(0.0080, 0.0004)
2010	Normal(0.0073, 0.0005)
2011	Normal(0.0066, 0.0005)
2012	Normal(0.0058, 0.0004)
2013	Normal(0.0051, 0.0004)
2014	Normal(0.0045, 0.0004)

Table A2.2 Proportion eligible to continue on ART after breastfeeding

CD4	ART for Health Eligibility Criteria				
	Option B			Option B+	
	< 250	< 350	< 500	< 350	< 500
≥500	0	0	0	1	1
350 - 499	0	0	1	1	1
200 - 349	Uniform(0.33, 0.50)	1	1	1	1
< 200	1	1	1	1	1

Table A2.3 Age – and calendar-specific fertility rates (US Census Bureau)

Year	Age			
	15-19	20-24	25-34	35-49
1977	0.1682	0.3384	0.3025	0.1440
1978	0.1682	0.3384	0.3025	0.1440
1979	0.1682	0.3384	0.3025	0.1440
1980	0.1682	0.3384	0.3025	0.1440
1981	0.1682	0.3384	0.3025	0.1440
1982	0.1682	0.3384	0.3025	0.1440
1983	0.1684	0.3309	0.2963	0.1420
1984	0.1686	0.3234	0.2901	0.1401
1985	0.1688	0.3159	0.2839	0.1382
1986	0.1690	0.3084	0.2776	0.1363
1987	0.1692	0.3009	0.2714	0.1344
1988	0.1694	0.2934	0.2652	0.1324
1989	0.1696	0.2945	0.2634	0.1295
1990	0.1699	0.2955	0.2616	0.1267
1991	0.1701	0.2966	0.2598	0.1238
1992	0.1703	0.2976	0.258	0.1209
1993	0.1706	0.2987	0.2563	0.1180
1994	0.1708	0.2997	0.2544	0.1151
1995	0.1711	0.3008	0.2527	0.1122

Table A2.3 Age – and calendar-specific fertility rates (US Census Bureau) (continued)

1996	0.1713	0.3018	0.2509	0.1093
1997	0.1715	0.3029	0.2491	0.1064
1998	0.1718	0.3039	0.2473	0.1036
1999	0.1720	0.3050	0.2455	0.1007
2000	0.1689	0.3003	0.2428	0.0990
2001	0.1666	0.2969	0.2409	0.0979
2002	0.1643	0.2936	0.2390	0.0968
2003	0.1621	0.2902	0.2371	0.0956
2004	0.1598	0.2868	0.2351	0.0944
2005	0.1598	0.2868	0.2351	0.0944
2006	0.1598	0.2868	0.2351	0.0944
2007	0.1598	0.2868	0.2351	0.0944
2008	0.1598	0.2868	0.2351	0.0944
2009	0.1578	0.2838	0.2334	0.0934
2010	0.1558	0.2808	0.2317	0.0924
2011	0.1538	0.2779	0.2300	0.0913
2012	0.1518	0.2749	0.2283	0.0903
2013	0.1499	0.2719	0.2266	0.0893
2014	0.1479	0.2689	0.2249	0.0883

Table A2.4 Mean duration of any breastfeeding (months)

	Year			
	1992	2000	2004	2010
Mean duration of breastfeeding	20.2	22.6	23.1	23.0

Table A2.5 Percent of pregnant women who received antenatal care from a skilled provider by age

Age	Year			
	1992	2000	2004	2010
15 -19	91.9	93.4	92.5	95.6
20 - 24	91.3	91.9	92.4	94.6
25 - 34	91.3	91.9	92.4	94.6
35 - 49	85.2	87.0	90.7	93.8

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